(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 362 002 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 89402373.8

(22) Date of filing: 31.08.89

(51) Int. Cl.5: C07K 5/02 , C07K 5/06 , C07K 5/08 , C07K 5/10 , C07K 7/02 , C07C 311/50 , C07C 311/51 , C07C 271/22 , C07C 271/20 , C07C 237/22 , C07C 237/10

(30) Priority: 01.09.88 EP 88402205

(43) Date of publication of application: 04.04.90 Bulletin 90/14

(84) Designated Contracting States: AT BE CH DE ES FR GB GR IT LI LU NL SE

(71) Applicant: MERRELL DOW PHARMACEUTICALS INC.
P.O. Box 156300 2110 East Galbraith Road
Cincinnati Ohio 45215-6300(US)

(72) Inventor: Schirlin, Daniel
12, rue Jean Jacques Rousseau Hoenheim
F-678000 Bischheim(FR)
Inventor: Pelton, John Tom
3, rue Murner
F-67000 Strasbourg(FR)
Inventor: Tarnus, Céline
43, rue du 22 Novembre
F-67000 Strasbourg(FR)
Inventor: Jung, Michel
3 Place Echauffour Engwiller
F-67350 Pfaffenhoffen(FR)

(74) Representative: Gillard, Marie-Louise et al
Cabinet Beau de Loménie 55, Rue d'Amsterdam
F-75008 Paris(FR)

(54) Novel peptidase inhibitors.

(57) This invention relates to analogs of peptidase substrates in which the nitrogen atom of the scissile amide bond of a partial retropeptide analog of the substrate has been replaced by a difluoromethylene moiety. These peptidase substrate analogs provide specific enzyme inhibitors for a variety of proteases, the inhibition of which exert valuable pharmacological activities and therefore have useful physiological consequences in a variety of disease states.

EP 0 362 002 A1

NOVEL PEPTIDASE INHIBITORS

This invention relates to protease enzyme inhibitors useful for a variety of physiological end-use applications.

In its broad aspects, this invention relates to analogs of peptidase substrates in which the nitrogen atom of the scissile amide bond of a partial retropeptide analog of the substrate has been replaced by a difluoromethylene moiety. These peptidase substrate analogs provide specific enzyme inhibitors for a variety of proteases, the inhibition of which exert valuable pharmacological activities and therefore have useful physiological consequences in a variety of disease states.

In its more specific aspects, this invention relates to activated electrophilic ketone retroamide analogs of certain peptidase substrates which are useful in inhibiting serine-, thiol-, carboxylic acid- and metallo-dependent proteolytic enzymes, the inhibition of which will have useful physiological consequences in a variety of disease states.

Still more specifically, this invention relates to activated electrophilic ketone retroamide analogs of peptidase substrates which fall within the following generic groupings characterized according to their active site dependencies. Such generic groupings are:

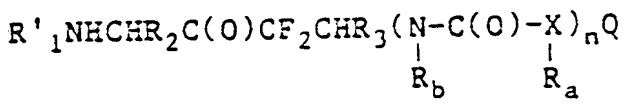
I. Serine Dependent Enzymes: These include such enzymes such as Elastase (human leukocyte), Cathepsin G, Thrombin, Plasmin, C-1 Esterase, C-3 Convertase, Urokinase, Plasminogen Activator, Acrosin, β-Lactamase, D-Alanine-D-Alanine Carboxypeptidase, Chymotrypsin, Trypsin and Kallikreins.

II. Thio Dependent Enzymes: Cathepsin B.

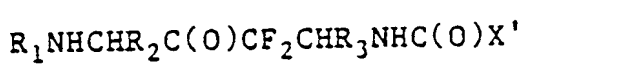
III. Carboxylic Acid Dependent Enzymes: These include such specific enzymes as Renin, Pepsin and Cathepsin D.

IV. Metallo Dependent Enzymes: These include Angiotensin Converting Enzyme, Enkephalinase, Pseudomonas Elastase and Leucine Aminopeptidase.

The contemplated peptidase inhibitors of the foregoing enzymes are compounds of the formulae



A



B

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein:

R'_1 is an α-amino protecting group selected from Group K', an α-amino acid or a peptide comprised of 2 to 8 α-amino acid units, said α-amino acid and peptide bearing a protecting group of Group K',

R_1 is hydrogen, an α-amino protecting group of Groups K' and K, an α-amino acid or a peptide comprised of 2 to 8 α-amino acid units, the terminal amine of said α-amino acid and peptide optionally bearing a protecting group of Groups K' and K,

R_2 is a side chain of the α-amino acid, a moiety of Group J or CHM which are responsible for directing the inhibitor to the active site of the enzyme,

R_3 is H, C_{1-7} alkyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 2-pyridylalkyl, or is a side chain of an α-amino acid for that peptidase substrate analog,

n is an integer of 1 to 10,

R_a is a side chain of an α-amino acid for that peptidase substrate analog, or is an ethylene moiety which when attached to the nitrogen atom of that retroamide forms a 2-oxopyrrolidine moiety,

R_b is H, C_{1-7} alkyl or an ethylene moiety which when linked to the CH moiety of X forms a 2-oxopyrrolidine moiety,

X is H, CH, OR_7 or R_7, with R_7 being a C_{1-7} alkyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl or 2-pyridylalkyl, with the proviso that when X is other than CH, R_a and Q are deleted,

X' is H, C_{1-7} alkyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 2-pyridylalkyl or an amino β halo C_{1-6} alkylene.

Q is H, C_{1-10} alkyl, C_{1-10} aralkyl, $C(O)R_5Y$ or C(O)Y,

R_5 is an α-amino acid or a peptide comprised of 2 to 5 α-amino acid units,

Y is NHR_4 or OR_4, and

R_4 is H, C_{1-7} alkyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl or 2-pyridylalkyl.

with CHM being an abbreviation for cyclohexylmethylene.

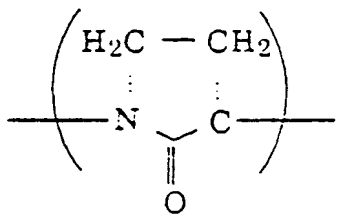
Isosteres of the compounds of formulae A and B include those wherein (a) one or more of the α-amino acid residues of the R_1 and Q substituents are in their unnatural configuration (when there is a natural configuration) or (b) when the normal peptidic carbamoyl linkage is modified, such as for example, to form $-CH_2NH-$ (reduced),

$-C-N(CH_3)$ (N-methylamide), $-COCH_2-$(keto), $-CH(OH)CH_2-$ (hydroxy), $-CH(NH_2)CH_2-$ (amino), $-CH_2CH_2-$ (hydrocarbon). Preferably a compound of the invention should not be in an isosteric form, particularly it is preferred that there be no modified peptidic carbamoyl group in the R_1 and Q radicals, but if there is, it is preferable to keep the isosteric modifications to a minimum.

A compound of the invention may be in free form, e.g., amphoteric form, or in salt, e.g., acid addition or anionic salt, form. A compound in free form may be converted into a salt form in an art-known manner and vice-versa. Examples of salt forms are the trifluoroacetate, hydrochloride, sodium, potassium and ammonium forms, although the scope of salts embraced herein is not limited thereto, the scope includes all of the salts known to be useful in the art of peptide chemistry.

Unless otherwise stated, the α-amino acid building blocks of these peptidase substrate analogs are preferably in their L-configuration. However, in those instances wherein there is an amide peptide bond between the CF_2 and a resulting malonyl moiety, then the α-amino acid building blocks between the CF_2 moiety and the malonyl moiety are in their D-configuration.

Before further defining and/or illustrating the scope of the peptidase inhibitors embraced by formulae A and B, it may be convenient to state some of the more basic concepts related to peptides. For example, except for proline, all of the α-amino acids found in proteins have as a common denominator a free carboxyl group and a free unsubstituted amino group on the α-carbon atom (in proline, since proline's α-amino group is substituted it is really an α-amino acid, but for convenience, it will also be spoken of as an α-amino group). Additionally, each α-amino acid has a characteristic "R-group", the R-group being the side chain, or residue, attached to the α-carbon atom of the α-amino acid. For example, the R-group residue for glycine is hydrogen, for alanine it is methyl, for valine it would be isopropyl. (Thus, throughout this specification the R_2, R_3 and R_a moieties are the side chains (or residues) for each indicated α-amino acid or are another radical which is defined for these sites for any given protease inhibitor.) For these specific side chains (or residues) of the involved α-amino acids reference to A.L. Lehninger's text on Biochemistry (particularly Chapter 4) would be helpful. In those instances wherein R_a is an ethylene moiety attached to the CH group of X and to the nitrogen atom of that retroamide, that resulting 2-oxo-pyrrolidine moiety is represented by



wherein the dotted lines depict the ethylene moiety attached to the retroamide.

As a further convenience for defining the scope of the compounds embraced by the generic concept of formulae A and B, as well as the sub-generic concepts relating to each of the individual enzymes involved in this invention, various α-amino acids have been classified into a variety of groups which impart similar functional characteristics for each of the specific enzymes to be inhibited by the peptidase substrates of formulae A and B. These groups are set forth in Table II and the recognized abbreviations for the α-amino acids are set forth in Table I.

TABLE I

AMINO ACID	SYMBOL
Alanine	Ala
Arginine	Arg
Aspargine	Asn
Aspartic acid	Asp
Asn + Asp	Asx
Cysteine	Cys
Glutamine	Gln
Glutamic acid	Glu
Gln + Glu	Glx
Glycine	Gly
Histidine	His
Isoleucine	Ile
Leucine	Leu
Lysine	Lys
Methionine	Met
Phenylalanine	Phe
Proline	Pro
Serine	Ser
Threonine	Thr
Tryptophan	Trp
Tyrosine	Tyr
Valine	Val
Norvaline	n-Val
Norleucine	n-Leu
1-Naphthylalanine	Nal(1)
2-Indolinecarboxylic acid	Ind
Sarcosin	Sar

TABLE II

Groups:

A: Lys and Arg
B: Glu, Asp
C: Ser, Thr, Gln, Asn, Cys, His, (3-pyrazolyl)Ala, (4-pyrimidinyl)Ala, and N-methyl derivatives
C': Ser, Thr, Gln, Asn and Cys, and their N-methyl derivatives.
D: Pro, Ind

E: Ala, β-Ala, Leu, Ile, Val, n-Val, β-Val, Met, CHM, β-Valine, β-Alanine, n-Leu and N-methyl derivatives (β- representing beta)

E′: Leu, Ile, n-Val, Met, n-Leu, CHM and their N-methyl derivatives.

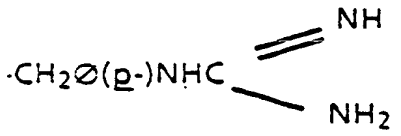
F: Phe, Tyr, CHM, O-Methyl Tyrosine, (3-pyrazolyl)Ala, (4-pyrimidinyl)Ala, Trp, Nal(1), and N-methyl derivatives

F′: Phe, Tyr, O-methyl tyrosine, Trp, Nal-(l) and their N-methyl derivatives.

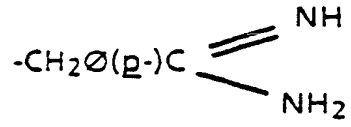
G: Gly, Sar

G′: Gly,

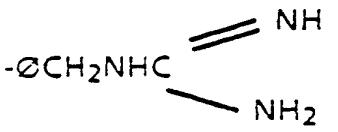
J:



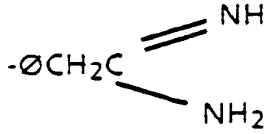
(J-1)



(J-2)



(J-3) and

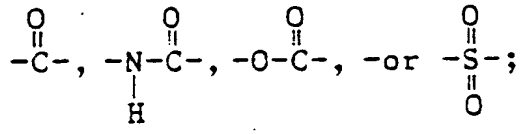


(J-4)

with ø, of course, representing phenyl (it being understood that the bond of J1-4 is always attached to an amino acid),

K: Acetyl (Ac), Succinyl (suc), Benzoyl(Bz), t-Butyloxycarbonyl(Boc), Carbobenzoxy(CBZ), Tosyl(Ts), Dansyl (DNS), Isovaleryl(Iva), Methoxysuccinyl(MeOSuc), 1-Adamantanesulphonyl($AdSO_2$), 1-Adamantaneacetyl (AdAc), 2-Carboxybenzoyl(2-CBZ), Phenylacetyl, t-Butylacetyl(Tba), bis[(1-naphthyl)methyl]acetyl (BNMA),

K′: is -A-Rz wherein A is



and Rz is an aryl group containing 6, 10 or 12 carbons suitably substituted by 1 to 3 members selected independently from the group consisting of fluoro, chloro, bromo, iodo, trifluormethyl, hydroxy, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and sulfonylaminocarbonyl) containing from 1 to 15 carbons, provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro.

In these instances wherein the normal R-group residue of an α-amino acid contains an -OH radical (e.g. serine, threonine and tyrosine), it is to be understood that such radical can be derivatized. For example, in each of the foregoing instances the -OH radical can be converted to an ether. When so-converted, such as for example to their methyl ethers, then such radicals will be referred to as O-methyl serine, O-methyl threonine and O-methyl tyrosine, respectively. These methyl ether-containing side chains may also be depicted as

$\dot{C}H_2OMe$, $H_3C\dot{H}\dot{C}$-OMe and $\dot{C}H_2Ø$-OMe(p), respectively. Similarly, other type derivatives (e.g., N-alkyl derivatives) may also be analogously represented.

In those instances wherein Group K′ represents an -A-Rz moiety, it is preferred that A represent -C-(=O)- and that Rz represent acylsulfonamido, particularly those wherein the acylsulfonamido contains an aryl moiety (preferably phenyl) substituted by a halogen. The preferred -A-Rz moieties being 4[-(4chlorophenyl)sulfonylaminocarbonyl]phenylcarbonyl, 4[(4bromophenyl)sulfonylaminocarbonyl]-phenylcarbonyl and 4[phenylsulfonylaminocarbonyl]phenylcarbonyl (said moieties being abbreviated as 4-Cl-ø-SAC-Bz, 4-Br-ø-SAC-Bz and ø-SAC-Bz, respectively). Further, for convenience in defining the scope of

the specific protease inhibitors of the sub-generic groups Ia through Iwb, the term "a ø-SAC-Bz" is meant to include 4-Cl-ø-SAC-Bz, 4-Br-ø-SAC-Bz and ø-SAC-Bz.

In those instances wherein the amino-protecting group as defined within Group K is restricted to the -A-R_z moiety, such moiety is designated as K′; K′ then being a sub-group of Group K which represents only those moieties defined by -A-R_z. In those instances wherein the terminal P-position (as distinguished from the P′-position) nitrogen atom can only bear an amino protecting group selected from Group K′, then the definition of R_1 will similarly be modified to R'_1. Thus, R'_1 is defined as an amino protecting group selected from Group K′, an α-amino acid or a peptide comprising a number of α-amino acids the terminal nitrogen atom of which bears a member of Group K′. (R_1, of course, being as previously defined in that the P-position terminal nitrogen atom may bear any of the Group K or K′ protecting groups as well as being an unprotected terminal amine, i.e., its protecting group is optional.)

As used herein the term "alkyl" includes the straight, branched-chain and cyclized manifestations thereof, particularly such moieties as methyl, ethyl, n-butyl, t-butyl, cyclopropyl, n-propyl, pentyl, cyclopentyl, n-hexyl, cyclohexyl and cyclohexylmethyl. The term "aralkyl" includes those aryl moieties attached to a C_{1-4} alkylene, preferably methyl or ethyl. The term "aryl" includes both carbocyclic and heterocyclic moieties. Preferred aralkyl and aryl moieties are phenyl, benzyl, naphthylmethyl, phenethyl, 2-pyridylmethyl.

In the instance wherein the X′-moiety of formula B is an amino β-halo C_{1-6} alkylene moiety, the alkylene bears one or two halogens, preferably fluoro, on a carbon atom to which the NH_2 group is not directly attached. Illustrative of the preferred radicals are: $-CH_2CH_2CH(CHF_2)NH_2$, $-CH_2CF_2NH_2$, $-CH_2CH(CHF_2)CH_2NH_2$ and $-CH_2$-CHF-CHF-CH_2NH_2.

In general the peptide of R'_1 and R_1 contains 2 to 8 α-amino acids, preferably 2 to 5. In those instances wherein Q represents $C(O)R_5Y$, with R_5 being an α-amino acid or a peptide, the peptide moiety may contain up to 5 α-amino acid units, although it is generally preferred to have 1, 2 or 3 α-amino acids. The scope of the number of

$$\left(\begin{array}{ccc} N & C & X \\ | & \| & | \\ R_b & O & R_a \end{array}\right)$$

units is from 1 to 10, but it is preferred that the number be less than 6, with one or two being most preferred.

The protease enzyme inhibitors of this invention are compounds of the formulae $R'_1NHCHR_2C(O)$-$CF_2CHR_3(NR_bC(O)XR_a)_nQ$ **A**

and

$R_1NHCHR_2C(O)CF_2CHR_3NHC(O)X'$ **B**

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R'_1 is an α-amino acid protecting group of Group K′, an α-amino acid or peptide comprised of 2 to 8 α-amino acid units, the terminal amine of said α-amino acid and peptide bearing a protecting group of Group K′,

R_1 is H, an α-amino protecting group of Groups K′ and K, an α-amino acid or a peptide comprised of 2 to 8 α-amino acid units, the terminal amine of said α-amino acid and peptide optionally bearing a protecting group of Groups K′ and K,

R_2 is a side chain of the α-amino acid, CHM or a moiety of Group J,

R_3 is H, C_{1-7} alkyl, phenyl, phenethyl, benzyl, cyclohexyl, cyclohexylmethyl, 2-pyridylalkyl, or is an α-amino acid side chain,

n is an integer of 1 to 10,

R_a is a side chain of an α-amino acid, CHM or is an ethylene moiety which when attached to the nitrogen atom of a retroamide forms a 2-oxopyrrolidine moiety,

R_b is H, C_{1-7} alkyl or an ethylene moiety when linked to the CH moiety of X forms a 2-oxopyrrolidine moiety,

X is H, CH, OR_7 or R_7, with R_7 being a C_{1-7} alkyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl or 2-pyridylalkyl, with the proviso that when X is other than CH, R_a and Q are deleted,

X′ is H, C_{1-7} alkyl, phenyl, phenethyl, benzyl, cyclohexyl, cyclohexylmethyl, 2-pyridylalkyl or an amino β halo C_{1-6} alkylene,

Q is H, C_{1-10} alkyl, C_{1-10} aralkyl, $C(O)R_5Y$ or C(O)Y,

R_5 is an α-amino acid or a peptide comprised of 2 to 5 α-amino acid units,

Y is NHR_4 or OR_4, and

R_4 is H, C_{1-7} alkyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl or 2-pyridylalkyl, and the α-amino acid or peptide moieties being selected from Groups A, B, C, C′, D, E, E′, F, F′, G, G′, J, K and K′, said groups being

A: Lys and Arg

B: Glu, Asp

C: Ser, Thr, Gln, Asn, Cys, His, (3-pyrazolyl)Ala, (4-pyrimidinyl)Ala, and N-methyl derivatives

C′: Ser, Thr, Gln, Asn and Cys, and their N-methyl derivatives,

D: Pro, Ind

E: Ala, β-Ala, Leu, Ile, Val, n-Val, β-Val, Met, CHM, β-Valine, β-Alanine, n-Leu and N-methyl derivatives (β- representing beta)

E′: Leu, Ile, n-Val, Met, n-Leu, CHM and their N-methyl derivatives,

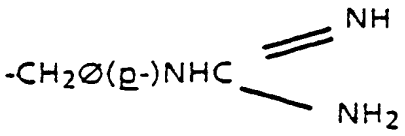
F: Phe, Tyr, CHM, O-Methyl Tyrosine, (3-pyrazolyl)Ala, (4-pyrimidinyl)Ala, Trp, Nal(1), and N-methyl derivatives

F′: Phe, Tyr, O-methyl tyrosine, Trp, Nal-(l) and their N-methyl derivatives,

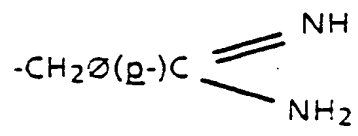
G: Gly, Sar

G′: Gly,

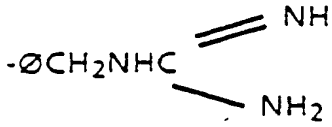
J:



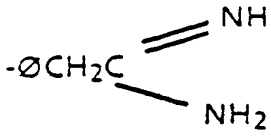
(J-1)



(J-2)



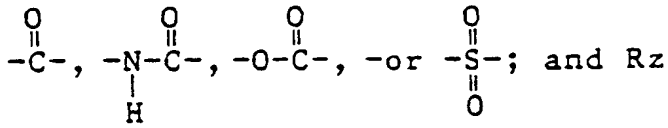
(J-3) and



(J-4)

K: Acetyl (Ac), Succinyl (suc), Benzoyl (Bz), t-Butyloxycarbonyl (Boc), Carbobenzoyl (CBZ), Tosyl (Ts), Dansyl (DNS), Isovaleryl (Iva), Methoxysuccinyl (MeOSuc), 1-Adamantanesulphonyl ($AdSO_2$), 1-Adamantaneacetyl (AdAc), 2-Carboxybenzoyl (2-CBZ), Phenylacetyl, t-Butylacetyl (Tba), bis [(1-naphthyl)-methyl]acetyl (BNMA),

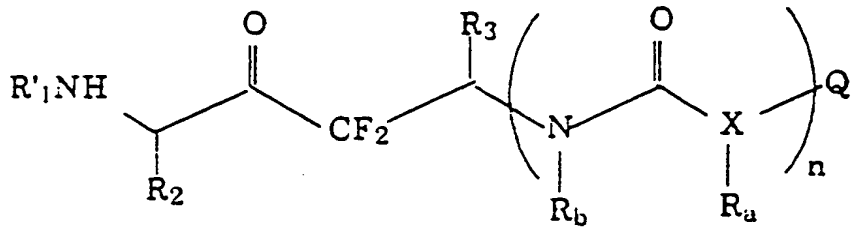
K′: is -A-Rz wherein A is



is an aryl group containing 6, 10 or 12 carbons suitably substituted by 1 to 3 members selected independently from the group consisting of fluoro, chloro, bromo, iodo, trifluormethyl, hydroxy, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido containing from 1 to 15 carbons, provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro.

Quite obviously the modifications to the scissile amide bond of the peptidase substrates of this invention presents certain nomenclature difficulties. In order to maintain a general consistency throughout this application the following explanations are offered to obviate any ambiguities relating to the scope and intent of this invention.

To better illustrate some aspects which may give rise to difficulties in nomenclature, an alternate expression of structural formula A is depicted in formula II as follows:



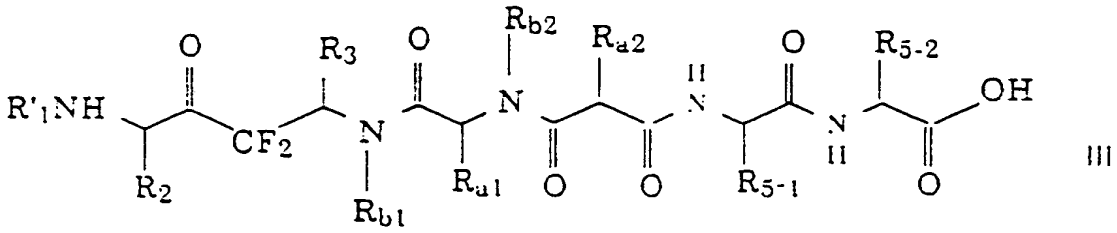
II

wherein R'_1, R_2, R_3, R_b, R_a, X, n and Q are as previously defined. In this depiction the R_2 moiety is in the P_1 position of the peptide, with R_2 representing the side chain of the P_1 α-amino acid, the α-amino acids of the R'_1 moiety would be in the P_2-->P_n positions, n being the numeric sequence dependent upon the number of α-amino acid building blocks in that particular compound, e.g., if R'_1 contained four α-amino acids it would be comprised of P_2-P_3-P_4-P_5 position having a terminal amino protecting group from Groups K' on the P_5 moiety. The CF_2 moiety has replaced the nitrogen atom of the P'_1 position. The position of the carbonyl of the P'_1 moiety has been reversed with the nitrogen of the P'_2 moiety resulting in a retroamide. The "CO" of the C(O)R_5Y or C(O)Y moieties of "Q" is the carbonyl of the contiguously adjacent moiety preceding the α-amino acid of R_5 (i.e., it is attached to the CH moiety when X is CH).

In the event n is 2 then there are two R_a moieties (i.e., R_{a1} and R_{a2}, each of which may be the same or different), if n is 3 then there are three R_a moieties, (i.e., R_{a1}, R_{a2} and R_{a3}) each of which may be the same or different and so on for each change in the definition of n. Analogously, the X and R_b moieties would similarly be increased (e.g., X_1, X_2, X_3, R_{b-1}, R_{b-2}, R_{b-3}) as n is increased, each being modified independently within the scope of their generic definitions.

In the instance wherein R_5 is comprised of two amino acids they may be referred to as R_{5-1} and R_{5-2}, or greater as the number of amino acids is increased. Preferably, however, the R_5 moiety contains no more than 5 α-amino acids with one or two being preferred when R_5 is not deleted.

Formula III is used to further illustrate the type compounds embraced by formula A and to more specifically illustrate the shorthand method of naming these compounds, as follows:



III

This formula illustrates a compound containing two retraomide moieties, a malonyl moiety, N-substitutions for R_b moieties, X being CH, n being 2, and Q being C(O)R_5Y with R_5 being a dipeptide moiety and Y being OH, which depiction may be written in accepted shorthand nomenclature as R'_1-R_2-[$CF_2R_3NR_{b-1}$](N-R_{b2}-R_{a1})-m-R_{a2}-R_{5-1}-R_{5-2}OH. Formula III makes it also apparent that the parenthesized oxygen atoms of formulae A and B are used to show that the function is a carbonyl moiety rather than have it confused with an ether linkage.

From formula III it is again quite obvious that the bracketed CF_2-retroamide inhibiting moiety is a moiety wherein the nitrogen atom of the α-amino acid has been replaced by a CF_2 radical, the R-residue remaining as defined for R_3 and the amide bond linking the two amino acids corresponding to the P'_1 and P'_2 positions has been reversed. Similarly, the amide bond linking the P'_2 and P'_3 positions has also been reversed. The brackets designate the retroamide moiety containing the CF_2 moiety, the parenthesis embracing the NR_{b2}-R_{a1} moiety indicates that it also is in a retroamide configuration and the underlined m - (i.e., meta) indicates a malonyl moiety containing the R_{a-2} α-amino acid side chain.

To further illustrate the shorthand nomenclature used throughout this application assume that R' is comprised of a P_2-P_3-P_4 moiety, the terminal amino protecting group being ø-SAC-Bz, P_2 is the amino acid Ala, P_3 is the amino acid Ala and P_4 is the amino acid Pro so that R'_1 is øSACBzProAlaAla, R_2 is the side chain of Val, R_3 is the side chain of Gly, R_b is ethyl, R_{a1} is H, R_{b2} is ethyl, R_{a2} is Gly, R_{5-1} is Val, R_{5-2} is Gly, then that specific compound would be written as øSACBzProAlaAlaVal[CF_2GlyN-Et](N-EtGly)m-GlyVal-GlyOH.

It is also to be noted that in some instances it is more convenient to designate the terminal amino

protecting group as a separate P_n position of the peptide, for example, in illustrative formula III. The terminal amino protecting group would be designated as being in the P_5 position and thus R'_1 would be P_2-P_3-P_4-P_5 with P_5 being a protecting group of Group K'. If P_4 optionally is an amino acid or is deleted, then quite obviously, when P_4 is deleted the protecting group would be attached to the P_3 moiety.

In light of the foregoing, the scope of the compounds of this invention, as defined in formulae A and B, for the inhibition of each of the involved specific enzymes are as defined in the following sub-generic formulae Ia through Iw-b.

Compounds of formula A which are useful as inhibitors of human leukocyte elastase are compounds of the formula

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ Ia

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R'_1 is $P_2P_3P_4$ having a Group K' protecting group on its terminal amine, preferably 4-Cl or 4-Brø-SAC-Bz or ø-SAC-Bz,

P_2 is an amino acid of Groups D, E and F, preferably Pro,

P_3 is an amino acid of Groups D and E and Lys, preferably Ile, Lys, Val or Ala,

P_4 is an amino acid of Group E or is zero, preferably Ala,

R_2 is a side chain of an amino acid of Groups E and G, preferably Val,

R_3 is a side chain of an amino acid of Groups E and G, preferably Gly or Ala,

R_a is a side chain of an amino of Groups E and G and Lys, preferably Ala, Phe, and

R_b, X, n and Q are as defined in formula A, preferably n is one, R_b is H, X is CH, and Q is H, C(O)Y or C-(O)R_5Y, preferably C(O)Y with Y being NH_2, alkyl (methyl, ethyl or propyl), benzyl, or O-alkyl (methyl, ethyl or propyl), and when present R_5 is an amino acid of Groups E and G, preferably Ala.

Human leukocyte elastase is released by polymorphonuclear leukocytes at sites of inflammation and thus is a contributing cause for a number of disease states. Thus the peptidase substrates of formula (Ia) have an anti-inflammatory effect useful in the treatment of gout, rheumatoid arthritis and other inflammatory diseases, and in the treatment of emphysema. In their end-use application the enzyme inhibitory properties of the compounds of (Ia) are readily ascertained by standard biochemical techniques well known in the art. Potential dose range for their end-use application will of course depend upon the nature and severity of the disease state as determined by the attending diagnostician with the range of 0.01 to 10 mg/kg body weight per day being useful for the aforementioned disease states with 0.1 mg to 10 mg/kg per day being preferred. The preferred compounds for this enzyme are:

4-Clø-SAC-Bz-Ala-Ala-Pro-Val-[CF_2GlyNH]m-Gly-NH_2,

4-Clø-SAC-Bz-Ala-Ile-Pro-Val[CF_2GlyNH]m-Ala-NH_2,

4-Clø-SAC-Bz[ϵN-2(CBZ)]-Lys-Pro-Val-[CF_2GlyNH]m-Ala-NH_2,

4-Clø-SAC-Bz-[ϵN-2(CBZ)]-Lys-Pro-Val-[CF_2GlyNH]m-Ala-OH,

4-Clø-SAC-Bz-[ϵN-2(CBZ)]-Lys-Pro-Val-[CF_2GlyNH]m-Ala-OMe,

4-Clø-SAC-Bz-Ala-Ala-Pro-Val-[CF_2GlyNH]C(O)CH_3,

ø-SAC-Bz-Val-Pro-Val[CF_2GlyNH]C(O)CH_2ø,

4-Clø-SAC-Bz-Val-Pro-Val-[CF_2GlyNH]C(O)CH_2ø,

4-Brø-SAC-Bz-Val-Pro-Val-[CF_2GlyNH]C(O)CH_2ø,

ø-SAC-Bz-Val-Pro-Val-[CF_2GlyNH]C(O)CH_2ø,

4-HOOCøC(O)-Val-Pro-Val-[CF_2GlyNH]C(O)CH_2ø, or

4-Clø-SAC-Bz-Val-Pro-Val-[CF_2GlyNH]C(O)CH_3.

Compounds of formula A which are useful as inhibitors of Cathepsin G are compounds of the formula

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ Ib

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R'_1 is $P_2P_3P_4$ having a Group K' protecting group on its terminal amine, preferably 4-Cl or 4-Brø-SAC-Bz or ø-SAC-Bz,

P_2 is an amino acid of Groups D, E and G, with proline being preferred,

P_3 is an amino acid of Groups E and G, or is deleted, with alanine being preferred,

P_4 is an amino acid of Groups E and G, or is deleted, with Ala being preferred,

R_2 is a side chain of an amino acid of Groups E and F, preferably Phe,

R_3 is as defined in formula A with the amino acid side chain selected from amino acids of Groups E and G, preferably Gly, Ala and Phe,

R_a, R_b, X, n and Q are as defined in formula A, preferably n is one, when X is CH, R_a is H and Q is H, and when X is other than CH, X is OR, R being alkyl, preferably methyl or ethyl, and R_b is H.

The end-use application of the compounds (Ib) inhibiting Cathepsin G is the same as for human leukocyte inhibitors, including arthritis, gout and emphysema, but also embracing the treatment of glomeru-

lonephritis and lung infestations caused by infections in the lungs. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ib) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 to 10 mg/kg per day being preferred. Preferred compounds for formula (Ib) are:

4-Clø-SAC-Bz-Ala-Ala-Pro-Phe-[CF_2-Gly-NH]C(O)CH_3,

4-Clø-SAC-Bz-Ala-Ala-Pro-Phe-[CF_2-Phe-NH]C(O)CH_3,

4-Clø-SAC-Bz-Ala-Ala-Pro-Phe-[CF_2-Ala-NH]C(O)$_2CH_3$,

4-Clø-SAC-Bz-Ala-Ala-Pro-Phe-[CF_2-Ala-NH]C(O)$_2$Et.

Those compounds of formula A which are useful as inhibitors of thrombin are compounds of the formula

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ Ic

and the hydrates, isosteres of pharmaceutically acceptable salts thereof, wherein

R'_1 is a protecting group of Group K', (a) P_2P_3 or (b) $P_2P_3P_4$ the terminal amine of (a) and (b) having a protecting group of Group K', preferably 4-Cl or 4-Brø-SAC-Bz or ø-SAC-Bz, with

(a) P_2 is an amino acid of Groups D, E and F, preferably Pro,

P_3 is an amino acid of Group F, preferably in its D-configuration with D-Phe being preferred,

(b) P_2 is an amino acid of Group E, preferably Ala,

P_3 is an amino acid of Groups C, E and G, preferably Ser,

P_4 is an amino acid of Groups E, F and G or is zero, preferably Phe, R_2 is a side chain of an amino acid of Group A, or a moiety of Group J, preferably Arg or J-1,

R_3 is as defined in formula A with the side chain of an amino acid being of Groups C and G, preferably Gly and Ser,

R_5 is an amino acid of Groups C', E and D or is zero, preferably zero,

R_a is a side chain of an amino acid of Groups C and G, preferably Gly and Ser,

R_b, X, n and Q are as defined for formula A, preferably R_b is H, n is one, X is CH, R_a is H and Q is alkyl, preferably methyl, ethyl and propyl.

The compounds embraced by formula (Ic) inhibit thrombin and therefore, as in the use of heparin, the compounds may be used as the initial anticoagulant agent in thrombophlebitis and coronary thrombosis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ic) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred. Preferred compounds are as expressed for Cathepsin G and also include:

4-Clø-SAC-Bz-(D)-Phe-Pro-JI-[CF_2-Gly-NH]C(O)C_3H_7,

4-Clø-SAC-Bz-(D)-Phe-Pro-Arg-[CF_2-Gly-NH]C(O)C_3H_7,

4-Clø-SAC-Bz-Arg-[CF_2-Gly-NH]C(O)C_3H_7,

4-Clø-SAC-Bz-Phe-Ser-Ala-[CF_2-Gly-NH]C(O)C_3H_7,

4-Clø-SAC-Bz-(D)-Phe-Pro-Lys-[CF_2-Gly-NH]C(O)CH_3,

4-Clø-SAC-Bz-JI-[CF_2-Gly-NH]C(O)CH_3.

Compounds of formula A which are useful as inhibitors of chymotrypsin are compounds of the formula

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ Id

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R'_1 is a protecting group of Group K' or $P_2P_3P_4$, the terminal amine of which bears a Group K' protecting group, preferably the protecting group is 4-Cl or 4-Brø-SAC-Bz or ø-SAC-Bz,

P_2 is an amino acid of Groups D, E and G or is deleted, preferably it is deleted or is Leu,

P_3 is an amino acid of Groups E and G or is deleted, preferably it is deleted or is Ala,

P_4 is an amino acid of Groups E and G or is deleted, preferably it is deleted or is Ala,

R_2 is a side chain of an amino acid of Groups E and F, preferably Phe or Tyr, and

R_3, R_a, R_b, X, n and Q are as defined in formula Ia, preferably R_b is H, n is one, X is CH, R_a is H, and Y is alkyl or O-alkyl, and R_3 is Gly.

The end-use application of the compounds (Id) inhibiting chymotrypsin is in the treatment of pancreatitis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Id) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course,

depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred. Preferred compounds are as expressed for Cathepsin G and also include:

4-Clø-SAC-Bz-Phe-[CF_2-Gly-NH]C(O)CH_3,
4-Clø-SAC-Bz-Phe-[CF_2-Gly-NH]C(O)Ome,
4-Clø-SAC-Bz-Tyr-[CF_2-Gly-NH]C(O)CH_3,
4-Clø-SAC-Bz-Tyr-[CF_2-Gly-NH]C(O)Ome,
CBZ-Leu-Phe-[CF_2Gly-NH]C(O)CH_3.

Compounds of formula A which are useful as inhibitors of trypsin are compounds of the formula

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ Ie

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R'_1 is a protecting group of Group K', P_2P_3 or $P_2P_3P_4$, the terminal amines of which bear a protecting group of Group K', preferably the Group K' protecting group is 4-Cl or 4-Brø-SAC-Bz or ø-SAC-Bz,

(a) P_2P_3 is

P_2 is an amino acid of Groups E and F, preferably in their D-configuration, preferably D-Pro or D-Ala,

P_3 is an amino acid of Group F, preferably in their D-configuration, preferably D-Phe,

(b) $P_2P_3P_4$ is

P_2 is an amino acid of Groups D and E, preferably in their D-configuration, preferably D-Pro or D-Ala,

P_3 is an amino acid of Groups E and G, preferably Ser,

P_4 is an amino acid of Groups E and G or is zero, preferably Phe, and R_2, R_3, R_a, R_b, n, X and Q are as defined in Ic.

The end-use application of the compounds (Ie) inhibiting trypsin is in the treatment of pancreatitis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ie) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg ot 10 mg/kg per day being preferred. The preferred compounds useful for inhibiting trypsin are the same as for the inhibitors of thrombin.

Compounds of formula A which are useful as inhibitors of plasmin are compounds of the formula

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ If

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R'_1 is P_2P_3, the terminal amine of which bears a protecting group of Group K', preferably 4-Cl or 4-Brø-SAC-Bz or ø-SAC-Bz,

P_2 is an amino acid of Groups E and F, preferably Ala or Phe,

P_3 is an amino acid of Groups B and F, preferably Glu,

R_2 is a side chain of an amino acid of Group A or a moiety of Group J, preferably Lys or J-I,

R_3, R_a, R_b, X, n and Q are as defined in formula Ia, preferably n is one, R_b is H, R_3 is Gly, R_a is Ala, Q is C-(O)Y with Y being alkyl (methyl or ethyl), OH, NH_2 or O-alkyl (methyl or ethyl).

The compounds embraced by formula (If) inhibit plasmin and are therefore anitproliferative agents useful in treating excessive cell growth, particularly in the treatment of benign prostatic hypertrophy and prostatic carcinoma, and in the treatment of psoriasis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (If) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 to 10 mg/kg per day being preferred. The preferred compounds are:

4-Clø-SAC-Bz-Glu-Phe-Lys[CF_2-Gly-NH]m-Ala-OH,
4-Clø-SAC-Bz-Glu-Phe-Lys[CF_2-Gly-NH]m-Ala-NH_2,
4-Clø-SAC-Bz-Glu-Phe-Lys[CF_2-Gly-NH]m-Ala-OCH_3,
4-Clø-SAC-Bz-Ala-J-I[CF_2-Gly-NH]$COCH_3$,
4-Clø-SAC-Bz-Ala-Lys-[CF_2-Gly-NH]$COCH_3$.

Compounds of formula A which are useful as inhibitors of C_1-esterase are compounds of the formula

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ Ig

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof wherein

R'_1 is P_2, the terminal amine of which bears a protecting group of Group K', preferably 4-Cl or 4-Brø-SAC-

Bz or ø-SAC-Bz,
P_2 is an amino acid of Groups A, B, C, D, E, F and G, preferably Ala,
R_2 is a side chain of an amino acid of Group A or a moiety of Group J, preferably Arg or J-I,
R_a is the side chain of an amino acid of Groups E and G, preferably Gly,
R_3, R_b, X, n and Q are as defined in formula A, preferably R_3 is a side chain of an amino acid of Groups E and G, preferably Gly, n is one, R_b is H, X is CH, R_a is Gly and Q is C(O)Y, Y preferably being alkyl (methyl or ethyl), O-alkyl (methyl or ethyl) or NH_2.

The compounds embraced by formula (Ig) inhibit C_2-esterase and are therefore useful in treating systemic lupus, arthritis, autoimmune hemolytic anemia and glomerulonephritis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ig) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred. The preferred compounds are:
4-Clø-SAC-Bz-Ala-Arg-[CF_2-Gly-NH]$COCH_3$,
4-Clø-SAC-Bz-Ala-Arg-[CF_2-Gly-NH]$COCCH_3$,
4-Clø-SAC-Bz-Ala-Arg-[CF_2-Gly-NH]m-Gly-NH_2,
4-Clø-SAC-Bz-Ala-J-I[CF_2-Gly-NH]$C\overline{O}CH_3$.

Compounds of formula A which are useful as inhibitors of C_3-convertase are compounds of the formula

$$R' : NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ \qquad Ih$$

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
R': is P_2P_3, the terminal amine of which bears a protecting group of Group K', preferably 4-Cl or 4-Brø-SAC-Bz or ø-SAC-Bz,
P_2 is an amino acid of Groups E and F, preferably Ala,
P_3 is an amino acid of Groups E and F, preferably Leu,
R_2 is a side chain of an amino acid of Group A or a moiety of Group J, preferably Arg,
R_3 is a side chain of an amino acid of Groups E or G, preferably Gly,
R_a is a side chain of an amino acid of Group E or Gly, preferably Gly or Ala,
R_b, X, n and Q are as defined in formula A, preferably n is one, R_b is H, X is CH, Q is C(O)Y with Y being NH_2, O-benzyl, alkyl (methyl or ethyl), O-alkyl (methyl or ethyl).

The compounds embraced by formula (Ih) inhibit C_3-convertase and are therefore useful in treating systemic lupus, arthritis, autoimmune hemolytic anemia and glomerulonephritis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ih) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred. The preferred compounds are:
4-Clø-SAC-Bz-Leu-Ala-Arg-[CF_2-Gly-NH]$COCH_3$,
4-Clø-SAC-Bz-Leu-Ala-Arg-[CF_2-Gly-NH]$COCCH_3$,
4-Clø-SAC-Bz-Leu-Ala-Arg-[CF_2-Gly-NH]COC-Benzyl,
4-Clø-SAC-Bz-Leu-Ala-Arg-[CF_2-Gly-NH]m-Ala-NH_2.

Compounds of formula A which are useful as inhibitors of Urokinase are compounds of the formula

$$R' : NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ \qquad Ii$$

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
R': is P_2P_3, the terminal amine of which bears a protecting group of Group K', preferably 4-Cl or 4-Brø-SAC-Bz or ø-SAC-Bz,
P_2 is an amino acid of Groups E and G, preferably Ala or Gly,
P_3 is an amino acid of Groups B, preferably Glu,
R_2 is a side chain of an amino acid of Group A or a moiety of Group J, preferably Arg,
R_3 is a side chain of an amino acid of Group E, preferably Ala,
R_a is a side chain of an amino acid of Group E, preferably Ala,
R_b, X, n and Q are as defined in formula A, preferably n is one or two, R_b (R_{b1} or R_{b2}) being H, X is CH and X_2 is CH or H, Q is H or C(O)Y with Y being NH_2, alkyl (methyl or ethyl) or O-alkyl (methyl or ethyl).

The compounds embraced by formula (Ii) inhibit Urokinase and therefore are useful in treating excessive cell growth disease states. As such compounds are useful in the treatment of benign prostatic hypertrophy and prostatic carcinoma, the treatment of psoriasis, and in their use as abortifacients. For their

end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ii) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1mg to 10 mg/kg per day being preferred. The preferred compounds are:

K′-Glu-Gly-Arg-[CF_2-Ala-NH]m-Ala-NH_2,

K′-Glu-Gly-Arg-[CF_2-Ala-NH](Ala)CHO,

K′-Glu-Gly-Arg-[CF_2-Ala-NH](Ala)$C(O)_2CH_3$,

K′-Glu-Gly-(p-gua)-Phe-[CF_2-Ala-NH](Ala)H,

(K′ being a protecting group, preferably 4-Clø-SAC-Bz).

Compounds of Formula A which are useful as inhibitors of plasminogen activator are compounds of the formula

R′$_1$NHCHR_2C(O)CF_2CHR_3(NR_b-C(O)XR_a)$_n$Q Ij

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R′$_1$ is P_2P_3, the terminal amine of which bears a protecting group from Group K′, preferably 4-Cl or 4-Brø-SAC-Bz or ø-SAC-Bz,

P_2 is Gly,

P_3 is an amino acid of Group B, preferably Glu,

R_2 is a side chain of an amino acid of Group A or a moiety of Group J, preferably Arg or J-1,

R_3 is a side chain of an amino acid of Groups E and F, preferably Phe or Ala,

R_a is a side chain of an amino acid of Group E, preferably Ala, and

R_b, X, n and Q are as defined in formula A, preferably R_b (R_{b1} and R_{b2}) is H, n is one or two, X is CH or H, and Q is H or C(O)Y with Y being NH_2.

The preferred compounds are:

4-Clø-SAC-Bz-Glu-Gly-Arg-[CF_2-Ala-NH](Ala)CHO,

4-Clø-SAC-Bz-Glu-Gly-(p-gua)-Phe-[CF_2-Ala-NH](Ala)H,

4-Clø-SAC-Bz-Glu-Gly-Arg-[CF_2-Ala-NH]m-Ala-NH_2.

The compounds embraced by formula (Ij) inhibit plasminogen activator and therefore are useful in treating excessive cell growth disease states such as, for example, being useful in the treatment of benign prostatic hypertrophy and prostatic carcinoma, in the treatment of psoriasis and in their use as abortifacients. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ij) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred

Compounds of formula A which are useful as inhibitors of acrosin are compounds of the formula

R′$_1$NHCHR_2C(O)CF_2CHR_3(NR_b-C(O)XR_a)$_n$Q Ik

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R′$_1$ is a protecting group of Group K′ or P_2P_3, the terminal amine of which bears a protecting group of Group K′, preferably the Group K′ protecting group is 4-Cl or 4-Brø-SAC-Bz or ø-SAC-Bz,

P_2 is an amino acid of Group E or is deleted, preferably Leu,

P_3 is an amino acid of Group E, or is deleted, preferably Leu,

R_2 is a side chain of an amino acid of Group A or a moiety of Group J, preferably Arg or J-1,

R_3 is a side chain of an amino acid of Groups E and G, preferably Gly,

R_a is a side chain of an amino acid of Group E, preferably Ala, and

R_b, X, n and Q are as defined in formula A, preferably R_b (R_{b1} and R_{b2}) is H, n is one or two, X is CH or H, and Q is H or C(O)Y with Y being OH or NH_2.

The preferred compounds are:

4-Clø-SAC-Bz-Leu-Leu-Arg-[CF_2-Gly-NH](Ala)CHO,

4-Clø-SAC-Bz-Leu-Leu-p-gua-Phe-[CF_2-Gly-NH]m-Ala-NH_2,

4-Clø-SAC-Bz-Leu-Leu-Arg-[CF_2-Gly-NH]m-Ala-OH,

4-Clø-SAC-Bz-Leu-Leu-Arg-[CF_2-Gly-NH]$COCH_3$,

4-Clø-SAC-Bz-J-I-[CF_2-Gly-NH]$COCH_3$.

The compounds of formula (Ik) are acrosin inhibitors and therefore are useful as anti-fertility agents in

that they possess the characteristics of preventing sperm from penetrating an otherwise fertilizable egg. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ik) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

Compounds of formula A which are useful as inhibitors of β-lactamase are compounds of the formula

R'_1-NHCHR_2C(O)CF_2CHR_3(NR_b-C(O)XR_a)$_n$Q II

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, with the proviso that the P_1 carbonyl moiety may exist in its chemically reduced form, wherein

R'_1 is a protecting group of Group K', preferably 4-Cl or 4-Brø-SAC-Bz or ø-SAC-Bz,

R_2 is a side chain of an amino acid of Groups C, E and G, preferably Gly,

R_3 is a side chain of an amino acid of Groups E and G, preferably Gly,

R_a, R_b, X, n and Q are as defined in formula A, preferably R_b is H, preferably n is one, R_a is H, X is CH and Q is H.

The preferred compounds are:

4-Clø-SAC-Bz-NHCH$_2$C(O)[CF_2-Gly-NH]COCH$_3$,

4-Clø-SAC-Bz-NHCH$_2$CHOH[CF_2-Gly-NH]COCH$_3$.

The compounds embraced by formula (II) inhibit β-lactamase and therefore are useful in the potentiation of antibacterial agents, particularly the β-lactam antibacterials. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (II) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

Compounds of formula A which are useful as inhibitors of D-Ala-D-Ala carboxypeptidase are compounds of the formula

R'_1-NHCHR_2C(O)CF_2CHR_3(NR_b-C(O)XR_a)$_n$Q Im

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R'_1 is P_2, the terminal amine of which bears a protecting group of Group K', preferably 4-Cl or 4-Brø-SAC-Bz or ø-SAC-Bz,

P_2 is N_ϵ-Ac-Lys or is an amino acid of Groups C and E, preferably N_ϵ-Ac-Lys,

R_2 is the side chain of D-Ala,

R_3 is a side chain of an amino acid of Group E, preferably D-Ala,

R_a, R_b, X, n and Q are as defined in formula A, preferably n is one or two, R_b (R_{b-1} and R_{b-2}) is H, R_a is Gly, X_1 is CH and X_2 is H; and Q is C(O)Y with Y being OH.

The preferred compounds are:

4-Clø-SAC-Bz-(N_ϵ-Ac-Lys)-D-Ala[CF_2-Ala-NH]CHO,

4-Clø-SAC-Bz-(N_ϵ-Ac-Lys)-D-Ala[CF_2-Ala-NH]m-Gly-OH.

The compounds embraced by formula (Im) are antibacterial agents particularly useful against gram negative organisms. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Im) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

Compounds of formula A which are useful as inhibitors of Cathepsin B are compounds of the formula

R'_1-NHCHR_2C(O)CF_2CHR_3(NR_b-C(O)XR_a)$_n$Q In

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R'_1 is P_2P_3, the terminal amine of which is a protecting group of Group K', preferably 4-Cl or 4-Brø-SAC-Bz or ø-SAC-Bz,

P_2 is an amino acid of Groups E and F, preferably Leu or Phe,

P_3 is an amino acid of Groups E and F or is deleted, preferably Leu,

R_2 is a side chain of an amino acid of Group A, Thr-O-Benzyl or a moiety of Group J, preferably Arg and J-1,

R_3 is a side chain of an amino acid of Groups E and G, preferably Gly,
R_a, R_b, X, n and Q are as defined for formula A, preferably n is one or two. R_b (R_{b-1} and R_{b-2}) is H, R_a is Gly, X_1 is CH and X_2 is H, and Q is C(O)Y with Y being OH.
The preferred compounds are:
4-Clø-SAC-Bz-Phe-J-l[CF_2-Gly-NH]$COCH_3$,
4-Clø-SAC-Bz-Leu-Leu-J-l[CF_2-Gly-NH]m-Gly-OH,
4-Clø-SAC-Bz-Leu-Leu-Arg[CF_2-Gly-NH]m-Gly-OH.

The compounds embraced by formula (In) inhibit Cathepsin B and therefore are useful in treating excessive cell growth disease states such as, for example, being useful in treating benign prostate hypertrophy, prostatic carcinoma, in treating psoriasis and in their use as abortifacients. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (In) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

Compounds of formula A which are useful as inhibitors of renin are compounds of the formula
$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ Io
and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, with the proviso that the carbonyl moiety of P_1 may exist in its chemically reduced form, wherein
R'_1 is $P_2P_3P_4P_5$, the terminal amine of which bears a protecting group of Group K', preferably 4-Cl or 4-Brø-SAC-Bz or ø-SAC-Bz,
P_2 is an amino acid, or its N-methyl derivatives of Groups C, E and F, (3-pyrazolyl)Ala or (4-pyrimidinyl)Ala, preferably His, n-Val, N-methyl-n-Val, N-methyl-n-Leu, or n-Leu, (3-pyrazolyl)Ala or (4-pyrimidinyl)Ala,
P_3 is an amino acid of Groups E and F, or is deleted, preferably Phe or O-methyl Tyr,
P_4 is an amino acid of Groups D, E and F, or is deleted, preferably Pro, β-Ala or β-Val,
P_5 is an amino acid of Groups C, E and F, or is deleted, preferably His or is deleted,
R_2 is a side chain of an amino acid of Groups E and F or CHM, preferably Leu or CHM,
R_3 is a side chain of an amino acid of Groups E and G, preferably Gly or Val,
R_a is a side chain of Groups E and G, preferably Val, Ile, Ala or Gly,
R_b, X, n and Q are as defined in formula A, preferably R_b is H, n is one or two, X_1 is CH and X_2 is benzyl, alkyl [preferably $(CH_2)_2$-$CH(CH_3)_2$, $CH(CH_3)_2$ or 1-(1-methyl propyl)-4-phenylbutyl], Q is C(O)Y, Y being NH-benzyl or NH-2-pyridylmethyl or Q is $C(O)R_5Y$ with R_{5-1} being an amino acid of Groups C, E and F with His preferred, and R_{5-2} is an amino acid of Groups C, E and Lys, or is deleted with Lys being preferred.
The preferred compounds are:
4-Clø-SAC-Bz-Na1(1)-His-Leu[CF_2-Gly-NH](Val)C(O)-Benzyl,
4-Clø-SAC-Bz-Na1(1)-His-Leu[CF_2-Gly-NH]m-Val-NH-Benzyl,
4-Clø-SAC-Bz-Phe-His-Leu-[CF_2-Gly-NH]m-Val-NH-Benzyl,
4-Clø-SAC-Bz-Phe-n-Val-Leu-[CF_2-Gly-NH]m-Val-NH-Benzyl,
4-Clø-SAC-Bz-Phe-n-Val-Leu-[CF_2-Gly-NH]m-Val-NH-Benzyl,
4-Clø-SAC-Bz-Phe-n-Val-Leu-[CF_2-Gly-NH]m-Ile-NH-2-pyridylmethyl,
4-Clø-SAC-Bz-His-Pro-Phe-His-Leu[CF_2-Val-NH]mIle-His-OH,
4-Clø-SAC-Bz-His-Pro-Phe-His-Leu[CF_2-Val-NH]m-Ile-His-NH_2,
4-Clø-SAC-Bz-Phe-His-CHM-[CF_2-Gly-NH](Val)C(O)-benzyl,
4-Clø-SAC-Bz-Phe-His-CHM-[CF_2-Gly-NH]m-Ile-NH-2-pyridylmethyl,
4-Clø-SAC-Bz-Phe-n-Val-Leu[CF_2-Gly-NH](Val)CO-benzyl,
4-Clø-SAC-Bz-His-Leu-[CF_2-Gly-NH]m-Val-NH-benzyl,
4-Clø-SAC-Bz-Phe-His-Leu[CF_2-Gly-NH]m-Val-NH-benzyl,
4-Clø-SAC-Bz-Phe-n-Val-Leu[CF_2-Gly-NH]m-Ala-NH-benzyl,
4-Clø-SAC-Bz-Phe-n-Val-Leu[CF_2-Gly-NH]m-Gly-NH-benzyl,
4-Clø-SAC-Bz-Phe-n-Val-Leu[CF_2-Gly-NH]Iva,
4-Clø-SAC-Bz-Phe-n-Val-Leu[CF_2-Gly-NH]CO_2(1-methylpropyl),
4-Clø-SAC-Bz-Phe-n-Val-CHM-[CF_2-Gly-NH]m-Val-NH-benzyl,
4-Clø-SAC-Bz-Phe-n-Val-CHM-[CF_2-Gly-NH]Iva,
4-Clø-SAC-Bz-Phe-n-Val-Leu-[CF_2-Gly-NH]CO[1-(1-methylpropyl)-4-phenylbutyl],
4-Clø-SAC-Bz-(0-Me)Tyr-n-Val-CHM-[CF_2-Val-NH]Iva,
4-Clø-SAC-Bz-Phe-(3-pyrazolyl)Ala-CHM-[CF_2-Val-NH]Iva.

4-Clø-SAC-Bz-(0-Me)Tyr-n-Val-CHM-[CF_2-Val-NH]Iva,
4-Clø-SAC-Bz-(0-Me)Tyr-(4-pyrimidinyl)Ala-CHM-[CF_2-Val-NH]Iva,
H-β-Ala-(OMe)Tyr-nVal-CHM[CF_2-Gly-NH]Iva,
H-β-Ala-(OMe)Tyr-nVal-CHM[CF_2-Val-NH]Iva,
H-β-Val-(OMe)Tyr-nVal-CHM[CF_2-Gly-NH]Iva,
H-β-Val-(OMe)Tyr-His-CHM[CF_2-Gly-NH]Iva,
H-β-Ala-(Ome)Tyr-His-CHM[CF_2-Gly-NH]Iva,
Iva-(OMe)-Tyr-nVal-CHM-[CF_2GlyNH]Iva,
Iva-(OMe)-Tyr-N-Me-nVal-CHM-[CF_2GlyNH]Iva,
Iva-Phe-(N-Me)nVal-CHM-[CF_2GlyNH]Iva,
H-β-Val-(OMe)Tyr-(N-Me)nVal-"CHM"[CF_2-Gly-NH]Iva,
with CHM being an abbreviation for cyclohexylmethylene.

The compounds of formula (Io) inhibit renin and therefore are used as antihypertensive agents useful in treating hypertension. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Io) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

Compounds of formula A which are useful as inhibitors of pepsin are compounds of the formula

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ Ip

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, with the proviso that the P_1 carbonyl moiety may exist in its chemically reduced form, wherein

R'_1 is P_2P_3, the terminal amine of which bears a protecting group of Group K', preferably 4-Cl or4-Brø-SAC-Bz or ø-SAC-Bz,
P_2 is an amino acid of Groups E and F, preferably Val,
P_3 is an amino acid of Groups E and F, or is deleted, preferably Val,
R_2 is a side chain of an amino acid of Groups E and F, preferably Leu,
R_3 is a side chain of an amino acid, preferably Gly,
R_a, R_b, X, n and Q are as defined in formula A, preferably R_b is H, R_a is a side chain of Group E (Ala preferred), n is one, X is CH and Q is C(O)Y with Y being NH alkyl [$(CH_2)_2CH(CH_3)_2$ or $-CH_2(CH_3)_2$ preferred].

The preferred compounds are:
4-Clø-SAC-Bz-Val-Leu[CF_2-Gly-NH](Ala)Iva,
4-Clø-SC-Bz-Val-Val-Leu[CF_2-Gly-NH](Ala)Iva,
4-Clø-SAC-Bz-Val-Leu[CF_2-Gly-NH]m-Ala-Iaa,
4-Clø-SAC-Bz-Val-Val-Leu[CF_2-Gly-NH]m-Ala-Iaa.

The compounds of formula (Ip) inhibit pepsin and therefore exert an antiulcer effect useful in the treatment and prevention of ulcers. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ip) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

Compounds of formula A which are useful as inhibitors of Cathepsin D are compounds of the formula

$R'_1NHCHR_2V(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ Iq

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R'_1 is P_2P_3, the terminal amine of which bears a protecting group of Group K', preferably 4-Cl or 4-Brø-SAC-Bz or ø-SAC-Bz,
P_2 is an amino acid of Groups E and F, preferably Val or Ala,
P_3 is an amino acid of Groups E and F or is deleted, preferably Val,
R_2 is a side chain of an amino acid of Groups E and F, preferably Phe,
R_3 is Gly or Phe,
R_a, R_b, X, n and Q are as defined in formula A, preferably n is one or two, X is CH, R_a is a side chain of Group E (preferably Ala), Q is H, C(O)Y or $C(O)R_5Y$, R_5 is an amino acid of Group F (Phe preferred) and Y is O-alkyl (methyl or ethyl preferred) or NH-alkyl [$NH(CH_2)_2CH(CH_3)_2$ or $-NHCH_2CH(CH_3)_2$ preferred].

The preferred compounds are:
4-Clø-SAC-Bz-Val-Val-Phe-[CF_2-Phe-NH](Ala)Iva,
4-Clø-SAC-Bz-Val-Val-Phe-[CF_2-Phe-NH]m-Ala-$NHCH_2CH(CH_3)_2$,
4-Clø-SAC-Bz-Val-Ala-Phe[CF_2-Gly-NH](Ala)Iva,
4-Clø-SAC-Bz-Val-Phe[CF_2-Gly-NH]m-Ala-Phe-OCH_3.

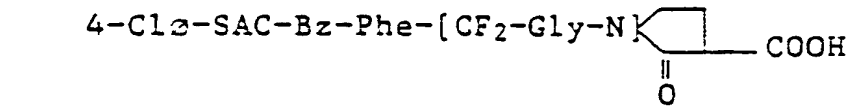
As inhibitors of Cathepsin D the compounds of formula (Iq) are useful for the same end-use applications set forth for human leukocyte elastase inhibitors (Ia) and are also useful as antidemyelinating agents useful to prevent and arrest nerve tissue damage. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (In) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

Compounds of formula A which are useful as inhibitors of angiotensin converting enzyme (ACE) are compounds of the formula

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ Ir

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
R'_1 is a protecting group of Group K', preferably 4-Cl or 4-Brø-SAC-Bz or ø-SAC-Bz,
R_2 is a side chain of an amino acid of Groups E, F and G, preferably Phe,
R_3 is a side chain of an amino acid of Groups E or Gly, preferably Gly or Ala,
R_a, R_b, X, n and Q are as defined in formula A, preferably R_b is H or CH_3, R_a is Gly or R_a and R_b, together with the N-C(O)-CH moiety forms a 2-oxopyrrolidine, n is one or two, X is CH and Q is C(O)Y with Y being OH.

The preferred compounds are:
4-Clø-SAC-Bz-Phe-[CF_2-Gly-NCH_3]m-Gly-OH,
4-Clø-SAC-Bz-Phe-[CF_2-Gly-NH]m-Gly-OH,



4-Clø-SAC-Bz-Phe-[CF_2-Ala-NH]m-Gly-OH.

The compounds of formula (Ir) inhibit ACE and are therefore useful as antihypertensives useful in treating hypertension. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ir) are readily ascertained by standard biochemical techniques well know in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

Comounds of formula A which are useful as inhibitors of enkephalinase are compounds of the formula

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ Is

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
R'_1 is P_2P_3, the terminal amine of which is a protecting group of Group K', preferably 4-Cl or 4-Brø-SAC-Bz or ø-SAC-Bz,
P_2 is Gly,
P_3 is an amino acid of Group F or is deleted, preferably Tyr,
R_2 is the side chain of Gly,
R_3 is the side chain of an amino acid of Group F, preferably Phe,
R_a, R_b, X, n and Q are as defined in formula A, preferably R_b is H, n is one or two, R_a is the side chain of Group E (Met or Leu preferred), X is CH and Q is C(O)Y with Y preferably being OH.
The preferred compounds are:
4-Clø-SAC-Bz-Tyr-Gly-Gly-[CF_2-Phe-NH]m-Met-OH,
4-Clø-SAC-Bz-Tyr-Gly-Gly-[CF_2-Phe-NH]m-Leu-OH.

The compounds of formula (Is) inhibit enkephalinase and therefore are useful as analgesics. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics

of the compounds of (Is) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

Compounds of formula A which are useful as inhibitors of pseudomonas elastase are compounds of the formula

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ It

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R'_1 is P_2, the terminal amine of which bears a protecting group of Group K', preferably 4-Clø-SAC-Bz, 4-Brø-SAC-Bz or ø-SAC-Bz,

P_2 is an amino acid of Group E, preferably Ala,

R_2 is a side chain of an amino acid of Groups E and G, preferably Ala,

R_3 is a side chain of an amino acid of Group E, preferably Leu,

R_a, R_b, X, n and Q are as defined for formula A, preferably R_a is a side chain of Group E (Ala preferred), R_b is H, n is one or two, Q is C(O)Y with Y being NH_2.

The preferred compound is:

4-Clø-SAC-Bz-Ala-Ala-[CF_2-Ile-NH]m-Ala-NH_2.

The compounds of formula (It) inhibit pseudomonas elastase and therefore are useful as antibacterial agents particularly useful against infections caused by pseudomonas bacteria. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (It) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

Compounds of formula A which are useful as inhibitors of leucine aminopeptidase are compounds of the formula

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ Iu

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R'_1 is a protecting group of Group K', preferably 4-Clø-SAC-Bz, 4-Brø-SAC-Bz or ø-SAC-Bz,

R_2 is a side chain of an amino acid of Groups A, B, E and F, a moiety of Group J or CHM, preferably CHM, Phe, Leu, Glu, Arg, J-1,

R_3 is a side chain of amino acids of Group E and Gly or CHM, preferably Ala, Gly or CHM,

R_a, R_b, X, n and Q are as defined for formula A, preferably R_a is a side chain of Group E, Gly or CHM (Ala, Gly and CHM preferred), R_b is H, n is one or two, X is CH and Q is C(O)Y with Y being benzyl, OH, NH benzyl, NH alkyl [-$(CH_2)_2CH(CH_3)_2$ or $CH_2CH(CH_3)_2$ preferred].

The preferred compounds are:

K'-Leu[CF_2-CHM-NH](Ala)Iva,

K'-Phe[CF_2-CHM-NH]m-Gly-OH,

H-CHM[CF_2-Ala-NH](Gly)Iva,

K'-Leu[CF_2-CHM-NH]m-Ala-NH-benzyl,

K'-Leu[CF_2-Gly-NH]m-CHM-NH-benzyl,

K'-Leu[CF_2-Gly-NH](CHM)CO-benzyl.

K' being one of 4-Cl or 4-Brø-SAC-Bz or ø-SAC-Bz.

The compounds of formula (Iu) are inhibitors of leucine amino peptidase and therefore are useful as immunostimulants useful in conjunctive therapy in the treatment with other known anticancer agents. For their end-use application, the potency and other biochemical parameters of the enzyme inhi biting characteristics of the compounds of (Iu) are readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

Compounds of formula A which are useful as inhibitors of kallikreins, tissue or plasma, are compounds of the formula

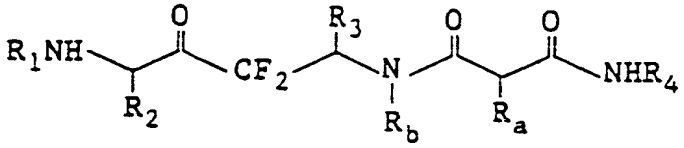
$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ Iv

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R'_1 is P_2P_3, the terminal amine of which bears a protecting group of Group K', preferably 4-Clø-SAC-Bz, 4-Brø-SAC-Bz or ø-SAC-Bz,
P_2 is an amino acid of Groups E and F, preferably Phe,
P_3 is an amino acid of Groups C, E and F, preferably in their D-configuration, D-Pro being most preferred,
R_2 is a side chain of an amino acid of Group A or a moiety of Group J, preferably Arg or J-1,
R_3 is the side chain of Gly,
R_a, R_b, X, n and Q are as defined for formula A, preferably R_a is H, R_b is H, n is one or two, X is CH or alkyl (methyl or ethyl) and Q is C(O)Y, Y being O-alkyl (methyl or ethyl) or NH_2.
The preferred compounds of this formula are:
4-Clø-SAC-Bz-(D)-Pro-Phe-Arg-[CF_2-Gly-NH]$COCH_3$,
4-Clø-SAC-Bz-(D)-Pro-Phe-Arg-[CF_2-Gly-NH]COOme,
4-Clø-SAC-Bz-(D)-Pro-Phe-Arg-[CF_2-Gly-NH]m-Gly-NH_2,
4-Clø-SAC-Bz-(D)-Pro-Phe-J-1-[CF_2-Gly-NH]$\overline{C}OCH_3$.

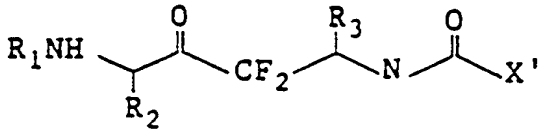
The compounds of formula (Iv) are inhibitors of the kallikreins, tissue or plasma, and therefore inhibit kinin formations. Kinins, generally known to induce pain and vascular permeability associated with inflammation and infection, e.g., bacterial and viral, the inhibition of the kinin formation renders these compounds useful in the alleviation of pain and inflammation. Furthermore, these compounds are useful as male contraceptives in that they will dramatically interfere with normal sperm function. In their end-use application dose range will be about 0.01 to 10 mg/kg per day for an effective therapeutic effect with 0.1 mg to 10 mg/kg per day being preferred.

Compounds of this invention which are useful as inhibitors of retroviral proteases required for replication, particularly the HIV-1 and HIV-2 viral proteases, the viruses putatively responsible for causing acquired immuno deficiency syndrome (AIDS) are compounds of the formulae



Iwa

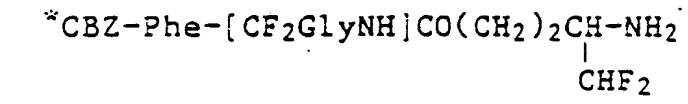
and



Iwb

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
R_1 is H, an amino protecting group of Groups K and K', or $P_2P_3P_4$ the terminal amines of which bear a protecting group of Groups K and K', preferably the amino protecting groups are Iva, Boc, CBZ, Tba, 4-Clø-SAC-Bz, 4-Brø-SAC-Bz or ø-SAC-Bz,
P_2 is an amino acid of Groups C', E', F' and G' or is deleted, preferably Asn, Gln and Ala,
P_3 is an amino acid of Groups C', E', F' and G' or is deleted, preferably Asn, Gln and Ala,
P_4 is an amino acid of Group C', β-Ala, β-Val or is deleted, preferably Ser, Thr, β-Ala or β-Val,
R_2 is the side chain of an amino acid of Groups E' and F' or CHM, preferably Phe, CHM, Tyr or Leu,.
R_3 is the side chain of an amino acid of Groups E' and G', preferably Gly and Ile,
R_a is the side chain of an amino acid of Group E' or Val, preferably Leu and Val,
R_b is H or C_{1-6} alkyl,
R_4 is H, C_{1-6} alkyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,
X' is amino-β-halo C_{1-6} alkylene or R_4, preferably amino-β-halo C_{1-6} alkylene is -$CH_2CH_2CH(CHF_2)NH_2$, -$CH_2CF_2CH_2NH_2$, -$CH_2CH(CHF_2)CH_2NH_2$, and -$CH_2CHFCHFCH_2NH_2$.
The preferred compounds of Formulae Iwa and Iwb are:
*Ser-Gln-Asn-Tyr[CF_2GlyNH]m-LeuNH_2,
*Thr-Gln-Asn-Tyr[CF_2GlyNH]$\overline{m}$-LeuNHCHM,
*Ser-Gln-Asn-Tyr[CF_2GlyNH]$\overline{C}$(O)H,
*Ser-Gln-Asn-Tyr[CF_2GlyNH]C(O)CHM,

*β-Ala-(O-Me)-Tyr-n-Val-CHM-[CF_2GlyNH]Iva,
*Boc-Phe-n-Val-CHM-[CF_2GlyNH]Iva,
*Iva-Ser-Gln-Asn-Tyr-[CF_2IleNH]Iva,
*Iva-Ser-Phe-n-Val-CHM-[CF_2GlyNH]Iva,
*Iva-Ser-Gln-Asn-Phe-[CF_2GlyNH]mValNH_2,
*Iva-Ser-Gln-Asn-Tyr-[CF_2IleNH]mValNH_2,
*CBZ-Phe-[CF_2GlyNH]C$OCH_2C_6H_5$,
*CBZ-Leu-[CF_2GlyNH](Val)C$OCH_2C_6H_5$,
*CBZ-Phe-nVal-Leu-[CF_2GlyNH]mValNH$CH_2C_6H_5$,
*Tba-Phe-nVal-Leu-[CF_2GlyNH]mValNH$CH_2C_6H_5$,
*H-Phe-nVal-CHM-[CF_2GlyNH]Iva,
*Iva-(Ome)-Tyr-nVal-CHM-[CF_2GlyNH]Iva,
*BOC-Phe-nVal-Leu-[CF_2GlyNH]Iva,
*CBZ-Phe-[CF_2GlyNH]C$O(CH_2)_3NH_2$,
*CBZ-Phe-[CF_2GlyNH]C$OCH_2CF_2CH_2NH_2$,



['In each instance the indicated protecting group (or H) may be replaced by a member of the group consisting of 4-Clø-SAC-Bz, 4-Brø-SAC-Bz, ø-SAC-Bz, Iva, Boc, CBZ and Tba.]

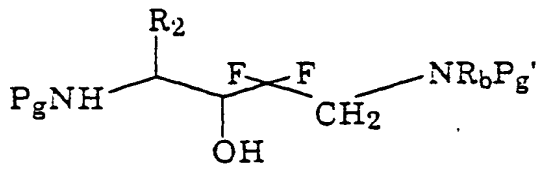
It is to be noted that when X' is amino β-halo-C_{1-6} alkyl, it is preferred that the halo be fluoro, preferably difluoro, and that the fluoro atoms cannot be on the carbon atom to which the NH_2 moiety is attached (see last named specific compound). Iva is the moiety -C(O)CH_2CHMe_2.

In their end-use application in the treatment of retroviral infections, the compounds of Formula Iwa and Iwb will be administered at about 1 to 100 mg per kilogram of body weight per day, preferably administered interperitoneally, intravenously and/or orally.

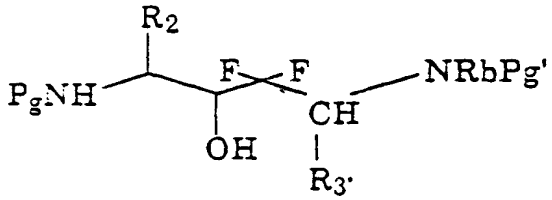
From the above, it is obvious that in all of the foregoing instances of (Ia) through (Iw), the definitions of R_3, R_b, R_a, X, n and Q are as defined in the generic formula I with the specific preferred embodiments being further illustrated for each group of enzyme inhibitors. Of course, it is also understood that in those instances wherein the carbonyl moiety of P_1 is in its reduced form, then such compounds are not hydrates.

Having defined the scope of the compounds within the generic invention and within the individual subgeneric groups for each of the individual enzymes, the manner in which such may be prepared will be described and illustrated.

In general, the compounds of formula I may be prepared using standard chemical reactions analogously known in the art. The key intermediates required for the application of standard peptide coupling techniques may be represented by the formula Va or Vb



Va

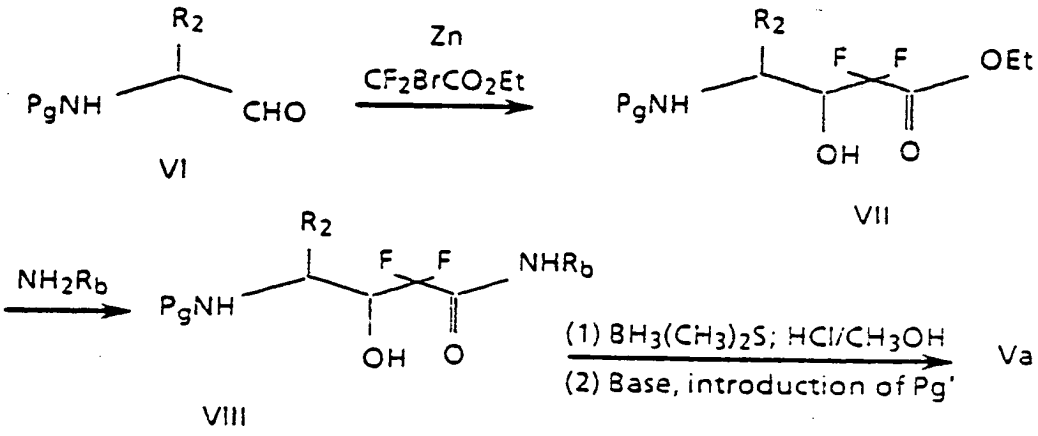


Vb

wherein
R'_3 is as defined for R_3 and may be a protected form of the residue of the specific α-amino acid involved,
R_2 is as previously defined, and
P_g and P_g' are each protecting groups, preferably different from each other so as to facilitate selective removal depending upon the site, nature and sequence of the reactions required to prepare the final compounds from these intermediates: the selection being according to principles well known and understood by those in the art.

In those instances wherein R'_3 represents hydrogen the preparation of the required intermediates (Va) is illustrated by Reaction Scheme A. In those instances wherein R'_3 is other than hydrogen then the required intermediates (Vb) are prepared by the methods depicted in Reaction Scheme B.

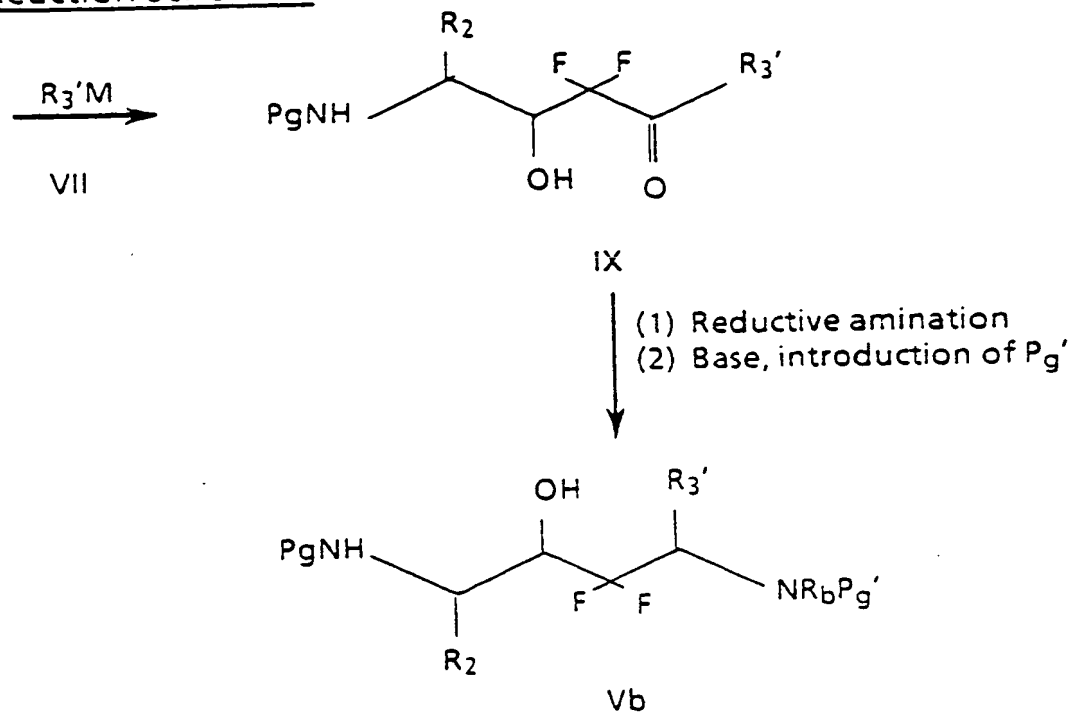
Reaction Scheme A



In effecting the steps of Reaction Scheme A it is preferred to start with the aldehyde of formula VI wherein the protecting group is a carbamate preferably wherein P_g is benzyloxycarbonyl (CBZ).This so-protected aldehyde is subjected to a condensation reaction with an ester of bromodifluoroacetic acid, preferably the ethyl ester in the presence of zinc. Preferably the reaction is conducted in an anhydrous aprotic solvent, e.g., tetrahydrofuran, ether, dimethoxyethane and the like under a nitrogen atmosphere. The reaction mixture is gently heated under reflux conditions, preferably to about 60°C for about 1-12 hours. The ester (VII) is converted to its primary amide (VIII) by treatment with liquid ammonia or R_bNH_2 under anhydrous conditions, preferably using such solvents as anhydrous diethyl ether. The addition of the R_bNH_2 or ammonia is initiated at -78°C and, following completion of the addition, the reaction mixture is slowly allowed to rise to room temperature. The so-formed amide is chemically reduced to form the free amine. This chemical reduction is easily effected by reacting the amide with a diborane, preferably as a diborane/dimethylsulfide complex, under a nitrogen atmosphere in an anhydrous aprotic solvent (e.g., THF) under reflux conditions. The reduction yields the desired amine, in the form of an acid (e.g., HCl) salt which by pH adjustment yields the free amine which may be suitably protected with an N-protecting group, e.g., P_g' is t-butoxy carbonyl using the standard reaction conditions (e.g., $(BOC)_2O$, tetrahydrofuran at room temperature) for protecting the amine. Alternatively the free amine may be subjected to reaction conditions designed to build the desired α-amino acid or peptide moiety on the "P' side of the difluoromethylene moiety.

In those instances where R'_3 is other than hydrogen then the procedure of Reaction Scheme A is modified to prepare the desired intermediates according to Reaction Scheme B.

Reaction Scheme B

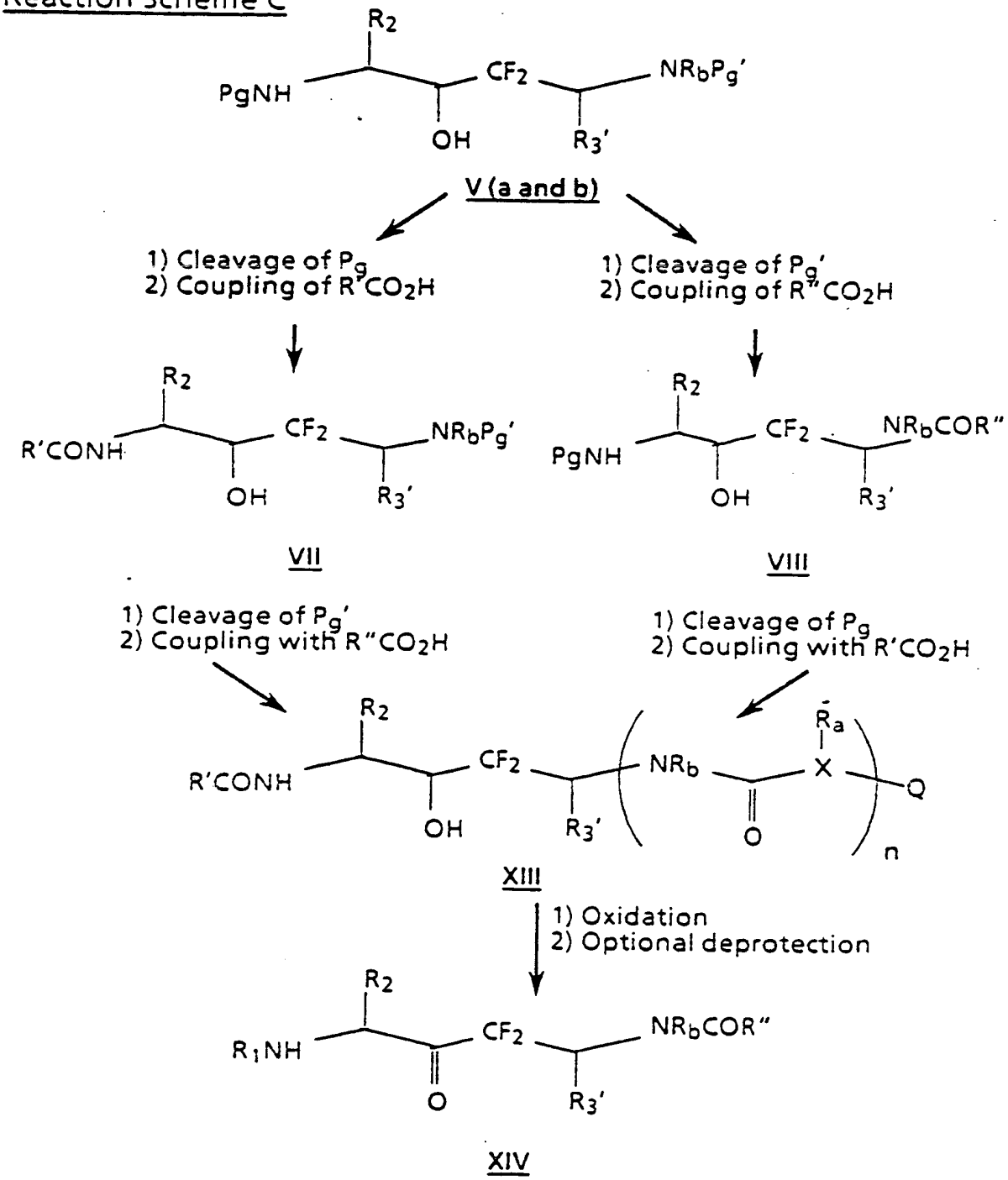


wherein R'_3M is an organometallic reagent, preferably lithium or magnesium coupled to the R'_3 moiety (other than hydrogen) desired.

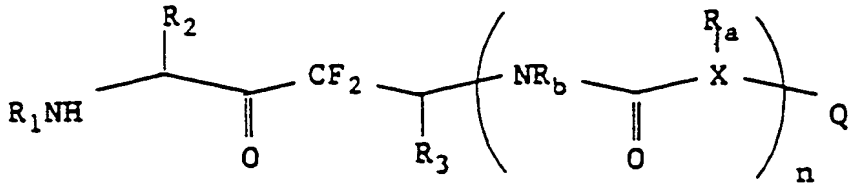
The conversion of the ester (VII) to the corresponding R'_3 bearing ketone with the organometallic reactant is effected by contacting the reactants together under anhydrous conditions at temperatures of about 0°-80° C in an aprotic solvent (e.g., tetrahydrofuran). Upon reaction the temperature is slowly allowed to rise to room temperature and the complex is hydrolysed to yield the desired intermediate ketones (IX) which compounds are subjected to reductive amination procedures well known in the art, such as, for example, the procedure described by Borch (see R.F. Borch, et al., J. Am. Chem. Soc., 93, 2897 (1971). This reductive amination can take place in one or two steps (with isolation of the intermediate imine or enamine). For example, reacting the ketones (IX) with ammonium acetate under slightly acidic conditions in methanol produces the enamine which, when reacted with sodium cyanoborohydride, produces the desired product. Alternatively, the ketones may be treated directly with sodium cyanoborohydride in the presence of ammonium acetate to produce the desired amines (as its HCl salts) which, in either case, may be neutralized and then the NHR_b or NH_2 moiety may be protected with an appropriate protecting group.

Having obtained the key intermediates of formula V (a and b) standard α-amino acid or peptide coupling procedures may be conducted to prepare the individual compounds of formula I. In practice it is more convenient to effect coupling on the P' side of the difluoromethylene moiety before coupling the P_2-P_n moieties because the CBZ protecting group is generally more stable and this facilitates a less difficult route of synthesis for the desired compounds. In general, this series of reactions may be depicted by Reaction Scheme C.

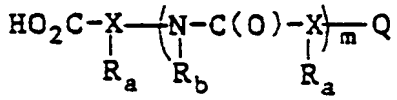
Reaction Scheme C



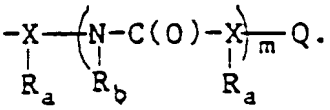
Formula XIV may otherwise be written as



wherein P_g, R_2, R_3, R_a, R_b, P_g' and R_1 are as previously defined, $R'CO_2H$ is the equivalent of R_1OH or R'_1OH (except, of course, in the instance wherein R_1 is H, coupling on the P-side of the molecule is obviated) and $R''CO_2H$ is the equivalent of

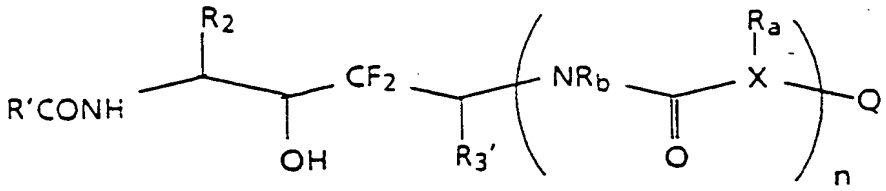


wherein m is n minus one,

i.e., R'' is  .

The oxidation may be effected via the well-known Swern oxidation procedure, or with a modified Jones reaction using pyridinium dichromate, or a chromic anhydride-pyridinium complex, or with 1,1,1-triacetoxy-2,1-benzoxiodol. Of course, if there are any protecting groups on the residues of the α-amino acid building blocks, such protecting groups may be removed after oxidation. The coupling procedures are effected according to standard procedures well known in the art.

In general the Swern oxidation is effected by reacting about 2 to 10 equivalents of dimethylsulfoxide (DMSO) with about 1 to 6 equivalents of trifluoromethylacetic anhydride [$(CF_3CO)_2O$] or oxalyl chloride [$(COCl)_2$], said reactants being dissolved in an inert solvent, e.g., methylene chloride (CH_2Cl_2), said reactor being under an inert atmosphere (e.g., nitrogen or equivalently functioning gas) under anhydrous conditions at temperatures of about -80°C to -50°C to form an *in situ* sulfonium adduct to which is added about 1 equivalent of the appropriate alcohols, i.e., from compounds VII and VIII by the coupling with $R''CO_2H$ and $R'CO_2H$, respectively, having the formula



XIII

Preferably, the alcohols are dissolved in an inert solvent, e.g., CH_2Cl_2 or minimum amounts of DMSO, and the reaction mixture is allowed to warm to about -50°C (for about 10-20 minutes) and then the reaction is completed by adding about 3 to 10 equivalents of a tertiary amine, e.g., triethylamine, N-methyl morpholine, etc.

In general, the modified Jones oxidation procedure may conveniently be effected by reacting the alcohols (XII) with pyridinium dichromate by contacting the reactants together in a water-tapping molecular sieve powder, e.g., a grounded 3 Angström molecular sieve), wherein said contact is in the presence of glacial acetic acid at about 0°C to 50°C, preferably at room temperature followed by isolation and then optionally removing amine protecting groups.

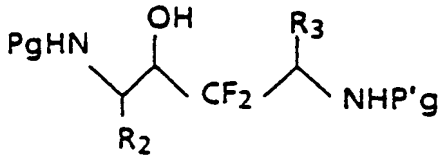
Alternatively, 1 to 5 equivalents of a chromic anhydride-pyridine complex (i.e., a Sarett reagent prepared *in situ* (see Fieser and Fieser "Reagents for Organic Synthesis" Vol. 1, pp. 145 and Sarett, et al.,

J.A.C.S. 25, 422, (1953)) said complex being prepared *in situ* in an inert solvent (e.g., CH_2Cl_2) in an inert atmosphere under anhydrous conditions at 0°C to 50°C to which complex is added 1 equivalent of the alcohols (XII) allowing the reactants to interact for about 1 to 15 hours, followed by isolation and optionally removing amine protecting groups.

Another alternative process for converting the alcohols (XII) to the desired ketones (XIII) is an oxidation reaction which employs periodane (i.e., 1,1,1-triacetoxy-2,1-benzoxiodol, (see Dess Martin, J. Org. Chem., 48, 4155 (1983)). This oxidation is effected by contacting about 1 equivalent of the alcohols (XII) with 1 to 5 equivalents of periodane (preferably 1.5 equivalents), said reagent being in suspension in an inert solvent (e.g., methylene chloride) under an inert atmosphere (preferably nitrogen) under anhydrous conditions at 0°C to 50°C (preferably room temperature) and allowing the reactants to interact for about 1 to 48 hours. Optional deprotection of the amine protecting groups may be effected as desired after the ketones have been isolated.

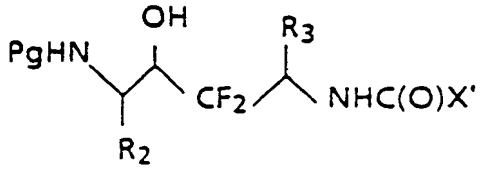
The preparation of the compounds of Formulae Iwa and Iwb follows the same general chemical pathways as outlined and described in Reaction Schemes A and B for the preparation of the key intermediates Va and Vb and also, with minor modifications, essentially follows the reaction pathways of Reaction Scheme C for those compounds wherein solid-phase chemistry is not required (i.e., for those compounds of Formula Iwb) and for those compounds which require solid-phase chemistry for the attachment of the R_1 moieties, the required intermediates (XIX) are prepared essentially along the same lines, with slight modifications, as outlined Reaction Scheme C in preparing compounds XIII. The preparation of the Iwa and Iwb compounds is more specifically illustrated in Reaction Schemes D and E: Scheme D being for those compounds of Iwb and Scheme E being for those compounds of Iwa.

Reaction Scheme D



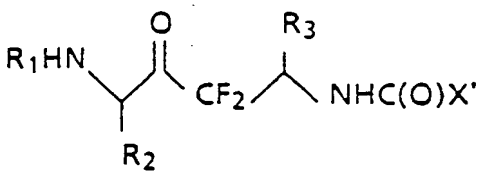
XV

(1) cleavage of P'g
(2) coupling with HOC(O)X'



XVI

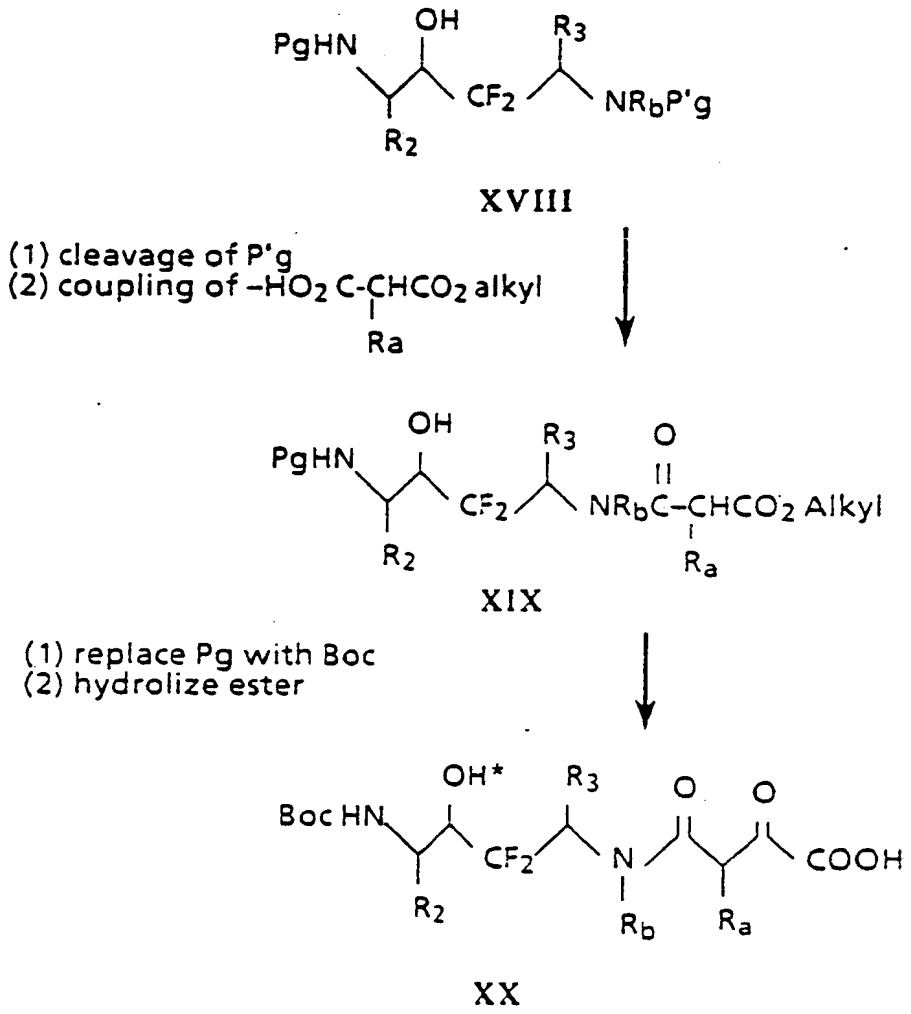
(3) remove Pg
(4) couple with R'CO_2H
(5) oxidation
(6) deprotection (optional)



XVII

wherein R_1, R_2, R_3, R'COOH and X' are as previously defined. Of course, the standard procedures outlined hereinabove for the cleavage of protecting groups, coupling, re-protecting and oxidation are applicable to the foregoing reaction scheme.

Reaction Scheme E



("or optionally oxidized) and wherein P'g, Pg, R_2, R_3, R_a, R_b are as previously defined above, said cleavage and/or replacing of protecting groups, hydrolysis (e.g., basic conditions) and oxidation procedures being those well-known in the art of peptide chemistry and/or as described above.

Following synthesis of the intermediates XX, compounds of Formula Iwa can be subjected to solid-phase sequential and block phase synthesis techniques in order to prepare compounds having the requisite R_1 moiety, and, of course, the hydroxy moiety, if not previously oxidized, may be oxidized by the modified Jones or Dess-Martin techniques described above, said oxidation preferably taking place while the compound is still on the resin.

The solid phase sequential procedure can be performed using established automated methods such as by use of an automated peptide synthesizer. In this procedure an amino protected amino group is bound to a resin support at the carboxy terminal end, the amino acid is deprotected at the amino position at which a peptide linkage is desired, the amino group neutralized with a base and the next amino protected amino acid in the desired sequence is coupled in a peptide linkage. The deprotection, neutralization and coupling steps are repeated until the desired polypeptide is synthesized. The compounds of the present invention are thus synthesized from their carboxy terminal end to their amino terminal end. The amino protected amino acid can be a conventional amino acid, a derivative or isomer thereof, or a spacer group. The resin support employed can be any suitable resin conventionally employed in the art for the solid phase preparation of polypeptides. The preferred resin is polystyrene which has been cross-linked with from about 0.5 to about 3% divinyl benzene, which has been either benzhydryl-amidated, chloromethylated or

hydroxymethylated to provide sites for amide or ester formation with the initially introduced amino protected amino acid.

An example of a hydroxymethyl resin is described by Bodansky et al. [Chem. Ind. (London) 38, 1597-98 (1966)]. The preparation of chloromethyl and benzhydrylamine resins are described by Stewart et al. ["Solid Phase Peptide Synthesis", 2nd Edition, Pierce Chemical Co., Rockford, Illinois (1984), Chapter 2, pp. 54-55]. Many of these resins are available commercially. In general, the amino protected amino acid which is desired on the carboxy-terminal end of the peptide is bound to the resin using standard procedures and practices as are well known and appreciated in the art. For example, the amino protected amino acid can be bound to the resin by the procedure of Gisin [Helv. Chem. Acta, 56, 1476 (1973)]. When it is desired to use a resin containing a benzhydrylamine moiety as the resin binding site an amino protected amino acid is coupled to the resin through an amide linkage between its α-carboxylic acid and the amino moiety of the resin. This coupling is effected using standard coupling procedures as described below. Many resin-bound amino acids are available commercially.

The α-amino protecting groups employed with each amino acid introduced into the polypeptide sequence may be any such protecting group known in the art. Among the classes of amino protecting groups contemplated are: (1) acyl type protecting groups such as formyl, trifluoroacetyl, phthalyl, p-toluenesulfonyl (tosyl), benzenesulfonyl, nitrophenylsulfenyl, tritylsulfenyl, o-nitrophenoxyacetyl, and α-chlorobutyryl; (2) aromatic urethane type protecting groups such as benzyloxycarbonyl and substituted benzyloxycarbonyl such as p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α-, α-dimethyl-3,5-dimethoxybennzyloxycarbonyl, and benzhydryloxycarbonyl; (3) aliphatic urethane protecting groups such as tert-butyloxycarbonyl (Boc), diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, and allyloxycarbonyl; (4) cycloalkyl urethane type protecting groups such as cyclopentyloxycarbonyl, adamantloxycarbonyl, and cyclohexyloxycarbonyl; (5) thio urethane type protecting groups such as phenylthiocarbonyl; (6) alkyl type protecting groups such as triphenylmethyl (trityl) and benzyl (Bzl); (7) trialkylsilane protecting groups such as trimethylsilane. The preferred α-amino protecting group is tert-butyloxycarbonyl (Boc). The use of Boc as an α-amino protecting group for amino acids is described by Bodansky et al. in "The Practice of Peptide Synthesis", Springer-Verlag, Berlin (1984), p. 20.

Following the coupling of the amino protected amino acid to the resin support, the α-amino protecting group is removed using any suitable procedure such as by using trifluoroacetic acid, trifluoroacetic acid in dichloromethane, or HCl in dioxane. The deprotection is carried out at a temperature of between 0 °C and room temperature. Other standard cleaving reagents may be used for removal of specific amino protecting groups under conditions well known and appreciated in the art.

After removal and neutralization of the α-amino protecting group the next desired amino-protected amino acid is coupled through a peptide linkage. This deprotection, neutralization and coupling procedure is repeated until a polypeptide of the desired sequence is obtained. Alternatively, multiple amino acid groups may be coupled by the solution method prior to coupling with the resin support amino acid sequence. The selection and use of an appropriate coupling reagent is within the skill of the ordinary practitioner in the art. Particularly suitable coupling reagents where the amino acid to be added is Gln, Asn, or Arg are N,N-dicyclohexylcarbodiimide and 1-hydroxybenzotriazole. The use of these reagents prevents nitrile and lactam formation. Other coupling agents are (1) carbodiimides (e.g., N,N-dicyclohexylcarbodiimide and N-ethyl-N'-(γ-dimethylaminopropylcarbodiimide); (3) ketenimines; (4) isoxazolium salts (e.g., N-ethyl-5-phenylisoxazolium-3-sulfonate); (5) monocyclic nitrogen containing heterocyclic amides of aromatic character containing one through four nitrogens in the ring such as imidazolides, pyrazolides, and 1,2,4-triazolides (specific heterocyclic amides that are useful include N,N-carbonyldiimidazole and N,N-carbonyl-di-1,2,4-triazole); (6) alkoxylated acetylene (e.g., ethoxyacetylene); (7) reagents which form a mixed anhydride with the carboxyl moiety of the amino acid (e.g., ethylchloroformate and isobutylcnloroformate) or the the symmetrical anhydride of the amino acid to be coupled (e.g., Boc-Ala-o-Ala-Boc); (8) nitrogen containing heterocyclic compounds having a hydroxy group on one ring nitrogen (e.g., N-hydroxyphthalimide, N-hydroxysuccinimide, and 1-hydroxybenzotriazole). Other activating reagents and their use in peptide coupling are described by Kapoor [J. Pharm. Sci., 59, 1-27 (1970)]. The generally preferred coupling method for the amino acids used in the present invention is the use of the symmetrical anhydride as the coupling agent.

The preferred coupling method for Gln, Asn and Arg is to react the protected amino acid, or derivatives or isomers thereof, with N,N-dicyclohexylcarbodiimide and 1-hydroxybenzotriazole (1:1) in N,N-dimethylformamide (DMF) in the presence of the resin or resin-bound amino acid or peptide. The preferred coupling method for other amino acids involves reacting the protected amino acid, or derivative or isomer thereof, with N,N-dicyclohexylcarbodiimide in dichloromethane to form the symmetrical anhydride. The symmetrical

anhydride in then introduced into the solid phase reactor containing the resin or resin-bound amino acid or peptide, and the coupling is carried out in a medium of DMF, or dichloromethane, or DMF:dichloromethane (1:1). A medium of DMF is preferred. The success of the coupling reaction at each stage of the synthesis is monitored by a ninhydrin test as described by Kaiser et al. [Analyt. Biochem. 34, 595 (1970)]. In cases where incomplete coupling occurs, the coupling procedure is repeated. If the coupling is still incomplete, the deprotected amine is capped with a suitable capping reagent to prevent its continued synthesis. Suitable capping reagents and the use thereof are well known and appreciated in the art. Examples of suitable capping reagents are acetic anhydride and acetylimidazole as described by Stewart et al. ["Solid Phase Peptide Synthesis", 2nd Ed., Pierce Chemical Co., Rockford, Ill. (1984), Chapter 2, p. 73].

After the desired amino acid sequence has been obtained, the peptide is cleaved from the resin. This can be effected by procedures which are well known and appreciated in the art, such as by hydrolysis of the ester or amide linkage to the resin. It is preferred to cleave the peptide from the benzhydrylamine resin with a solution of dimethyl sulfide, p-cresol, thiocresol, or anisole in anhydrous hydrogen fluoride. The cleavage reaction is preferably carried out at temperatures between about 0 °C and about room temperature, and is allowed to continue preferably from between about 5 minutes to about 5 hours.

As is known in the art of solid phase peptide synthesis, many of the amino acids bear side chain functionalities requiring protection during the preparation of the peptide. The selection and use of an appropriate protecting group for these side chain functionalities is within the ability of those skilled in the art and will depend upon the amino acid to be protected and the presence of other protected amino acid residues in the peptide. The selection of such a side chain protecting group is critical in that it must not be removed during the deprotection and coupling steps of the synthesis. For example, when Boc is used as the α-amino protecting group, the following side chain protecting groups are suitable: p-toluenesulfonyl (tosyl) moieties can be used to protect the amino side chains of amino acids such as Lys and Arg; p-methylbenzyl, acetamidomethyl, benzyl (Bzl), or t-butylsulfonyl moieties can be used to protect the sulfide containing side chains of amino acids such as cysteine, homocysteine, penicillamine and the like or derivatives thereof; benzyl (Bzl) or cyclohexyl ester moieties can be used to protect carboxylic acid side chains of amino acids such as Asp, Glu; a benzyl (Bzl) ether can be used to protect the hydroxy containing side chains of amino acids such as Ser and Thr; and a 2-bromocarbobenzoxy (2Br-Z) moiety can be used to protect the hydroxy containing side chains of amino acids such as Tyr. These side chain protecting groups are added and removed according to standard practices and procedures well known in the art. It is preferred to deprotect these side chain protecting groups with a solution of anisole in anhydrous hydrogen fluoride (1:10). Typically, deprotection of side chain protecting groups is performed after the peptide chain synthesis is complete but these groups can alternatively be removed at any other appropriate time. It is preferred to deprotect these side chains at the same time as the peptide is cleaved from the resin.

The compounds are then isolated and purified by standard techniques. The desired amino acids, derivatives and isomers thereof can be obtained commercially or can be synthesized according to standard practices and procedures well known in the art.

The following specific examples are given to illustrate the preparation of this invention although the scope of compounds is meant to be limiting to the scope of compounds embraced by formula I.

EXAMPLE 1

4-Benzyloxycarbonylamino-2.2-difluoro-3-hydroxy-6-methylheptanoic acid, ethyl ester

A mixture of 2.080 g (8.3 mmol) of L-N-benzyloxycarbonyl Leucinal and 2.230 g (11 mmol) of ethyl bromodifluoroacetate in dry THF (15 ml) was added dropwise to a refluxing suspension of 0.710 g of activated zinc wool in dry tetrahydrofuran (10 ml), under nitrogen. The addition rate was adjusted to maintain gentle reflux of the mixture. After the addition was complete, the solution was stirred for 3 hours at room temperature. The mixture was quenched by addition of 20 ml ethyl acetate, brine and 1M $KHSO_4$ (20 ml). The aqueous layer was dried over anhydrous $MgSO_4$, evaporated and purified by flash chromatography (silica gel, ethyl acetate/ cyclohexane, 1:9). 1.130 g of the expected ester were isolated (yield: 36%) (colorless oil).

Rf: 0.57 (ethyl acetate/cyclohexane, 1:1).

EXAMPLE 2

4-Benzyloxycarbonylamino-2,2-difluoro-3-hydroxy-6-methylheptanamide

A stream of dry ammonia was bubbled at -78°C, through a solution of 0.820 g (2.2 mmol) of 4-benzyloxycarbonylamino-2,2-difluoro-3-hydroxy-6-methylheptanoic acid, ethyl ester in anhydrous diethyl ether (10 ml). After saturation, the temperature was allowed to rise to room temperature with stirring. The excess ammonia was removed, and the solvent evaporated *in vacuo*. The residue was taken off in pentane to yield the expected amide in quantitative yield as a solid.
MS(Cl/NH_3): 345 (MH^+).

EXAMPLE 3

N^4-Benzyloxycarbonyl-N^1-tert-butoxycarbonyl-2,2-difluoro3-hydroxy-6-methyl-1,4-heptanediamine

A solution of 1M $BH_3/(CH_3)_2S$ (1 ml) in dichloromethane was added, under nitrogen, to a mixture of 0.185 g (0.53 mmol) of 4-benzyloxycarbonylamino-2,2-difluoro-3-hydroxy-6-methylheptanamide in anhydrous tetrahydrofuran (10 ml). The mixture was heated at reflux for 3 hours. After cooling to room temperature, methanol (3 ml) and 1N HCl in diethyl ether (6 ml) were added. The solvent was removed *in vacuo*. The residue was taken off in water and the aqueous layer washed with diethyl ether. The pH of the aqueous phase was adjusted to 10. Diethyl ether extraction afforded the intermediate amine which was directly converted to its N-BOC protected form [$(BOC)_2O$ 1.5 eq;tetrahydrofuran; room temperature]. The expected tert.-butylcarbamate was purified by chromatography (silica gel, ethyl acetate/cyclohexane, 1:1). 0.180 g (79% yield).
RF: 0.63 (ethyl acetate/cyclohexane, (1:1).

EXAMPLE 4

N^4-Benzyloxycarbonyl-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine, trifluoroacetate

A solution of 0.320 g (0.75 mmol) of N^4-benzyloxycarbonyl-N^1-tert-butoxycarbonyl-2,2-difluoro-3-hydroxy-6-methyl-1,3-heptanediamine in trifluoroacetic acid (5 ml) was stirred at 0°C for 30 minutes. The solvent was then removed *in vacuo*, and the residual oil taken off several times in diethyl ether and evaporated to dryness. The expected amine was obtained in quantitative yield and used in the next step without further purification. The pure free amine was isolated through the following procedure: washing the ethereal solution of the trifluoroacetate salt with saturated sodium bicarbonate (three times). The organic phase was dried over anhydrous magnesium sulphate. Filtration and removal of the solvent *in vacuo* left the expected pure N^4-benzyloxycarbonyl-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine as a white solid. (78% yield).

Analysis calculated for $C_{16}H_{24}N_2O_3F_2$			
found	C%: 58.17; C%: 57.66;	H%: 7.32; H%: 7.18;	N%: 8.48 N%: 8.31

EXAMPLE 5

N^4-Benzyloxycarbonyl-2,2-difluoro-3-hydroxy-N^1-(2-isovalerylamino-propionyl)-6-methyl-1,4-heptanediamine

To a stirred solution of 0.130 g (0.75 mmol) of N-isovaleryl-D-alanine in dry acetonitrile (5 ml), under nitrogen, was added 0.075 g (0.75 mmol) of N-methylmorpholine. The resultant solution was cooled to -20° C. Isobutyl chloroformate (0.103 g: 0.75 mmol) was added dropwise to the cooled reaction mixture. After 10 minutes, a mixture of 0.333 g (0.75 mmol) of N4-benzyl-oxycarbonyl-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine, trifluoroacetate and 0.080 g of N-methylmorpholine in dry dimethylformamide (5 ml) was added to the cooled mixture. After stirring for 4 hours at -20° C, the temperature of the mixture was allowed to rise to room temperature. Stirring was continued for 15 hours at room temperature. The mixture was then concentrated and placed under high vacuum to remove all the dimethylformamide. The resultant residue was chromatographed (silica gel, ethyl acetate) to give the expected peptide in 65% yield.
Rf: 0.13 (ethyl acetate/cyclohexane, 1:1).

Analysis calculated for $C_{24}H_{37}N_3O_5F_2$			
found	C%: 59.36; C%:59.72;	H%: 7.68; H%: 7.72;	N%: 8.65 N%: 8.54.

EXAMPLE 6

2,2-Difluoro-3-hydroxy-N^1-(2-isovalerylaminopropionyl)-6-methyl-1,4-heptanediamine

A solution of 0.192 g (0.39 mmol) of N^4-benzyloxycarbonyl-2,2-difluoro-3-hydroxy-N^1-2-(isovalerylaminopropionyl)-6-methyl-1,3-heptanediamine in ethanol (20 ml) was stirred at room temperature, in the presence of 10% Palladium on charcoal (0.010 g) under a hydrogen atmosphere for 5 hours. The hydrogen atmosphere was then replaced by a nitrogen atmosphere and the catalyst was filtered. The solvent was removed *in vacuo* leaving 0.125 g of a white solid (82% yield).

EXAMPLE 7

2,2-Difluoro-3-hydroxy-N^4-(2-isovalerylaminoisovaleryl)-N^1-(2-isovalerylaminopropionyl)-6-methyl-1,3-heptanediamine

The title compound was obtained from the amine of Example 6 and N-isovaleryl-L-valine by the procedure described in Example 5.
Rf: 0.45 (methanol/chloroform, 8:92).
MS(Cl/NH_3): 535 (MH^+).

EXAMPLE 8

2,2-Difluoro-N^4-(2-isovalerylaminoisovaleryl)-N^1-(2-isovalerylaminopropionyl)-6-methyl-3-oxo-1,4-heptanediamine

A solution of 0.024 g (0.045 mmol) of 2,2-difluoro-3-hydroxy-N^4-(2-isovalerylaminoisovaleryl)-N^1-(2-isovalerylaminopropionyl)-6-methyl-1,4-heptanediamine in methylene chloride (5 ml) was added to a suspension of pyridinium dichromate (0.026 g) and 3A molecular sieves (0.038 g), containing 4 µliters of glacial acetic acid. Stirring was continued for 15 hours at room temperature. Florisil (0.080 g) was added, stirring

continued for 15 minutes and the mixture filtered over sand. Removal of the solvent and chromatography (silica gel, ethyl acetate/acetone, 7:3) afforded the expected difluoroketone as a white solid (0.013 g; 55% yield).
Rf: 0.46 (methanol/chloroform 8:92)
MS(Cl/NH_3): 532 (M^+).

EXAMPLE 9

N^4-Benzyloxycarbonyl-2,2-difluoro-3-hydroxy-N^1-(2-isopentylaminocarbonylpropionyl)-6-methyl-1,4-heptanediamine

To a solution of 0.155 g (0.82 mmol) of 2-isopentylaminocarbonylpropanoic acid, 0.126 g of 1-hydroxybenzotriazole-H_2O and 0.169 g of N,N'-dicyclohexylcarbodiimide in anhydrous methylene chloride (5 ml), at 0° C was added a mixture of 0.363 g (0.82 mmol) of N^4-benzyloxycarbonyl-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine, trifluoroacetate and 0.083 g (0.82 mmol) of N-methylmorpholine in methylene chloride (3 ml). The cooling bath was removed after 1 hour and the reaction was stirred at room temperature overnight. The reaction mixture was then filtered and the filtrate was concentrated in vacuo. The expected peptide was isolated in 83% yield (0.340 g) after column chromatography purification (silica gel, ethyl acetate/chloroform, 1:1).
Rf: 0.16 (ethyl acetate/chloroform, 1:1).

Analysis calculated for $C_{25}H_{39}N_3O_5F_2$			
found	C%: 60.10; C%: 60.26;	H%: 7.87; H%: 7.81;	N%: 8.41 N%: 8.33.

EXAMPLE 10

2,2-Difluoro-3-hydroxy-N^1-(2-isopentylaminocarbonylpropionyl)-6-methyl-1,4-heptanediamine

The title compound was prepared from the peptide of Example 9 by the procedure described in Example 6 (96% yield).

EXAMPLE 11

2,2-Difluoro-3-hydroxy-N^4-(2-isovalerylaminoisovaleryl)-N^1-(2-isopentylaminocarbonylpropionyl)-6-methyl-1,4-heptanediamine

The title compound was prepared from the amine of Example 10 and N-isovaleryl-L-valine by the procedure described in Example 9.
Rf: 0.41 (methanol/chloroform, 8:92)
MS(Cl/NH_3): 549 (MH^+).

EXAMPLE 12

2,2-Difluoro-N^4-(2-isovalerylaminoisovaleryl)-N^1-(2-isopentylaminocarbonylpropionyl)-6-methyl-3-oxo-1,4-heptanediamine

The title compound was prepared from the alcohol of Example 11 by the procedure described in Example 8 (75% yield).
MS(Cl/NH_3): 547 (MH^+).

EXAMPLE 13

4-Benzyloxycarbonylamino-2,2-difluoro-3-hydroxy-5-phenylpentanoic acid, ethyl ester

The title compound was prepared from L-N-benzyloxy-carbonylphenylalaninal and ethyl bromodifluoroacetate by the procedure described in Example 1 (75% yield).
Rf: 0.5 (ethyl acetate/cyclohexane, 1:1).

Analysis calculated for $C_{21}H_{23}NO_5F_2$			
found	C%: 61.91; C%: 62.19;	H%: 5.69; H%: 5.75;	N%: 3.44 N%: 3.55

EXAMPLE 14

4-Benzyloxycarbonylamino-2,2-difluoro-3-hydroxy-5-phenylpentanamide

The title compound was prepared from the ester of Example 13 by the procedure described in Example 2 (98% yield).

EXAMPLE 15

N^4-Benzyloxycarbonyl-N1-tert-butoxycarbonyl-2,2-difluoro-3-hydroxy-5-phenyl-1,4-pentanediamine

The title compound was prepared from the amide of Example 14 by the procedure described in Example 3 (64% yield).

EXAMPLE 16

N^1-tert-Butoxycarbonyl-2,2-difluoro-3-hydroxy-5-phenyl-1,4-pentanediamine

The title compound was prepared in quantitative yield from the dicarbamate of Example 15 by the procedure described in Example 6.

EXAMPLE 17

N^4-Benzoyl-N^1-tert-butoxycarbonyl-2,2-difluoro-3-hydroxy-5-phenyl-1,4-pentanediamine

A solution of 0.330 g (1.03 mmol) of N^1-tert-butoxy-carbonyl-2,2-difluoro-3-hydroxy-5-phenyl-1,4-pentanediamine and 0.145 g benzoyl chloride (1.03 mmol) in anhydrous tetrahydrofuran was stirred at room temperature for 14 hours in the presence of 0.101 g triethylamine (1 mmol). The solvent was removed *in vacuo*. The residue was taken off in a mixture of methylene chloride and water. The organic phase was dried over $MgSO_4$. Evaporation and recrystallization from ethyl acetate/pentane afforded the expected compound as a white solid.

Analysis calculated for $C_{23}H_{28}N_2O_4F_2$			
found	C%: 63.58; C%: 63.68;	H%: 6.49; H%: 5.75;	N%: 6.45 N%: 6.85

EXAMPLE 18

N^4-Benzoyl-2,2-difluoro-3-hydroxy-5-phenyl-1,4-pentanediamine, trifluoroacetate

The title compound was prepared in quantiative yield from the product of Example 17 by the procedure of Example 4.

EXAMPLE 19

N^1-Acetyl-N4-benzoyl-2,2-difluoro-3-hydroxy-5-phenyl-1,4-pentanediamine

The title compound was prepared from the amine of Example 18 and acetic anhydride by the procedure described in Example 17 in the presence of 2 equivalents of N-methyl-morpholine.
MS(CI/NH_3: 377 (MH^+).

EXAMPLE 20

N^1-Acetyl-N4-benzoyl-2,2-difluoro-3-oxo-5-phenyl-1,4-pentanediamine

The title compound was prepared from the alcohol of Example 19 by the procedure described in Example 8.
Rf: 0.25 (methanol/chloroform, 8:92).
MS(CI/NH_3): 375 (MH^+).

EXAMPLE 21

4-Benzyloxycarbonylamino-2,2-difluoro-3-hydroxy-5-methylhexanoic acid, ethyl ester

The title compound was prepared from L-N-benzyloxycarbonylvalinal and ethyl bromodifluoroacetate by the procedure described in Example 1. (40% yield)

EXAMPLE 22

4-Benzyloxycarbonylamino-2,2-difluoro-3-hydroxy-5-methylhexanamide

The title compound was prepared in quantiative yield from the ester of Example 21 by the procedure described in Example 2.

EXAMPLE 23

N^4-Benzyloxycarbonyl-N^1-tert-butoxycarbonyl-2,2-difluoro-3-hydroxy-5-methyl-1,4-hexanediamine

The title compound was prepared from the amide of Example 22 by the procedure described in Example 3(yield:40%).
Rf: 0.50 (ethyl acetate/cyclohexane, 1:1).

EXAMPLE 24

N^1-tert-Butoxycarbonyl-2,2-difluoro-3-hydroxy-5-methyl-1,4-hexanediamine

The title compound was prepared in quantitative yield from the dicarbamate of Example 23 by the procedure described in Example 6.

EXAMPLE 25

N1-tert-Butoxycarbonyl-2,2-difluoro-3-hydroxy-N^4-(methoxysuccinyl-L-alanyl-L-alanyl-L-prolyl)-5-methyl-1,4-hexanediamine

The title compound was prepared from the amide of Example 24 and methoxy succinyl-L-alanyl-L-alnanyl-L-proline by the procedure described in Example 5 (yield: 48%).

EXAMPLE 26

2,2-Difluoro-3-hydroxy-N^4-[methoxysuccinyl-L-alanyl-L-alanyl-L-prolyl]-5-methyl-1,4-hexanediamine, trifluoroacetate

The title compound was prepared in quantitative yield from the product of Example 25 by the procedure described in Example 4.

EXAMPLE 27

2,2-Difluoro-3-hydroxy-N^4-[methoxysuccinyl-L-alanyl-L-alanyl-L-prolyl]-5-methyl-N^1-(2-methylmalonamoyl)-

1,4-hexanediamine

The title compound was prepared from the amine salt of Example 26 and 2-methylmalonamic acid by the procedure described in Example 9.

EXAMPLE 28

2,2-Difluoro-N^4-[methoxysuccinyl-L-alanyl-L-alanyl-L-prolyl]-5-methyl-N^1-(2-methylmalonamoyl)-3-oxo-1,4-hexanediamine

The title compound was prepared from the alcohol of Example 27 by the procedure described in Example 8.

EXAMPLE 29

5-Benzyloxycarbonylamino-3,3-difluoro-4-hydroxy-7-methyl-2-octanone

A 1.6 M solution of methyllithium in 1 ml of diethyl ether was added at -78° C to a solution of 0.195 g 4-benzyloxycarbonylamino-2,2-difluoro-3-hydroxy-6-methylheptanoic acid, ethyl ester (0.5 mmol) in 5 ml dry tetrahydrofuran. After stirring for 1 hour at -78° C, the temperature was allowed to rise to room temperature. Stirring was continued for 3 hours at room temperature. The mixture was hydrolyzed and extracted with diethyl ether. The organic layer was washed with brine and dried over $MgSO_4$. Filtation and removal of the solvent, in vacuo, left an oil, purified by column chromatography (silica gel, ethyl acetate/ cyclohexane, 2:8). 0.080 g of the expected ketone was thus isolated as a colorless oil (yield 47%).
Rf: 0.56 (ethyl acetate/cyclohexane, 1:1).

EXAMPLE 30

N5-Benzyloxycarbonyl-N2-tert-butoxycarbonyl-3,3-difluoro-4-hydroxy-7-methyl-2,5-octanediamine

A mixture of 0.080 g 5-benzyloxycarbonylamino-3,3-difluoro-4-hydroxy-7-methyl-2-octanone (0.23 mmol),0.177 g ammonium acetate (2.3 mmol), and 0.010 g sodium cyanoborohydride (0.16 mmol) in 3 ml methanol was stirred at room temperature, under nitrogen, for 20 hours. The mixture was acidified by addition of 1N HCl (2 ml) and the solvent removed *in vacuo*. The residue was taken off in water, the aqueous phase was washed with diethyl ether. The pH of the aqueous phase was adjusted to 10. Diethyl ether afforded the intermediate amine which was directly converted to its N-BOC protected form. [$(BOC)_2O$, 1.5 equivalent; tetrahydrofuran; room temperature]. The expected dicarbamate was purified by chromatography (silica gel, ethyl acetate/ cyclohexane, 1:1).

EXAMPLE 31

N^1-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N^4-(benzyloxycarbonyl)-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared from the amine of Example 4 and 2-benzylaminocarbonyl-3-methylbutanoic acid by the procedure described in Example 9 (yield: 55%)

Rf: 0.60 (ethyl acetate)
MS(CI/NH_3): 548 (MH^+).

Analysis calculated for $C_{29}H_{39}N_3O_5F_2$			
found	C%: 63.60; C%: 63.71;	H%: 7.18; H%: 7.10;	N%: 7.67 N%: 7.44.

EXAMPLE 32

N^1-(2-Benzylaminocarbonyl-3-methylbutanoyl)-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared from the compound of Example 31 by the procedure described in Example 6 (yield: 97%).

EXAMPLE 33

N^1-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N^4-[N-benzyloxycarbonyl-N^{im}-tert-butoxycarbonyl-L-Histidyl]-2,2-di-fluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared from N-benzyloxycarbonyl-N^{im}-tert-butoxycarbonyl-L-Histidine and the amine of Example 32 by the procedure described in Example 5 (yield: 64%).
Rf: 0.35 (ethyl acetate).
MS: (CI/NH_3): 785 (MH^+)

EXAMPLE 34

N1-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N4-Nim-tertbutoxycarbonyl-L-histidyl)-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared from the compound of Example 33 by the procedure described in Example 6 (yield: 90%).

EXAMPLE 35

N^1-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N^4-[[N-Benzyloxycarbonyl-3-(1-naphthyl)alanyl]-Nim-tert-butoxycarbonyl-L-histidyl]-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared from N-benzyloxycarbonyl-3-(1-naphthyl)alanine and the amine of Example 34 by the procedure described in Example 5 (yield: 77%).

EXAMPLE 36

N^1-(2-Benzylaminocarbonyl-3-methylbutanol)-N^4-[N-(benzyloxycarbonyl)-L-Phenylalanyl-Nim-tert-butoxycarbonyl-L-histidyl]-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptane-diamine

The title compound was prepared from N-benzyloxycarbonyl-L-phenylalanine and the amine of Example 34 by the procedure described in Example 5 (yield: 60%).

EXAMPLE 37

N^1-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N^4-[N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared from N-(tert-butoxy carbonyl)-L-phenylalanyl-L-n-valine and the amine of Example 32 by the procedure described in Example 5 (yield: 58%).
Rf: 0.56 (methanol/chloroform 8:92).
MS(Cl/NH_3): 760 (MH^+).

EXAMPLE 38

N^1-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N^4-[N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine

The title compound was prepared in 70% yield from the alcohol of Example 37 by the procedure described in Example 8.
Rf: 0.62 (methanol/chloroform 8:92)
MS(Cl/NH_3): 758(MH^+).

EXAMPLE 39

N^1-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N^4-[N-(benzyloxycarbonyl)-L-phenylalanyl-N^{im}-(tert-butoxycarbonyl)-L-histidyl]-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine

The title compound was prepared in 63% yield from the alcohol of Example 36 by the procedure described in Example 8.
Rf: 0.29 (ethyl acetate)
MS(Cl/NH_3): 930(MH^+).

EXAMPLE 40

N^1-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N^4-[N-(benzyloxycarbonyl)-L-phenylalanyl-L-histidyl]-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine

A mixture of 0.035 g (0.04 mmol) of N^1-(2-benzylaminocarbonyl-3-methylbutanoyl)-N^4-[N-(benzyloxycarbonyl)-L-phenyl alanyl-N^{im}-(tert-butoxycarbonyl)-L-histidyl]-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine and trifluoro acetic acid (5 mL) was stirred at 0° C for one hour. The solvent was removed *in vacuo*. The residue was taken off in ethyl acetate. The organic solution was washed with 5% sodium bicarbonate and dried over anhydrous magnesium sulphate. Filtration, removal of the solvent *in vacuo* and

purification by flash chromatography (silica gel; chloroform/methanol 96:2 to 92:8) yielded 0.019 g of the title compound as a white solid (61% yield).
MS(DCI/Cl + /NH_3): 830(MH^+,90); 722(83); 683(100); 649(21); 575(70); 504(76).

EXAMPLE 41

N^4-Benzyloxycarbonyl-2.2-difluoro-3-hydroxy-6-methyl-N^1-(3-methyl-2R-phenylacetylaminobutanoyl)-1.4-heptanediamine

The title compound was prepared in 38% yield from the amine of Example 4 and N-phenylacetyl-D-valine by the procedure described in Example 9.
Rf: 0.52 (silica gel; ethyl acetate)
Ms: 565(MNH^+_4, 57); 548(MH^+, 38); 457(85); 440(63); 414(100); 324(11).

EXAMPLE 42

2.2-Difluoro-3-hydroxy-6-methyl-N^1-(3-methyl-2R-phenylacetylaminobutanoyl)-1.4-heptanediamine

The title compound was prepared in 63% yield from the carbamate of Example 41 by the procedure described in Example 6.

EXAMPLE 43

N^4-[N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-2.2-difluoro-3-hydroxy-6-methyl-N^1-(3-methyl-2R-phenylacetylaminobutanoyl)-1.4-heptanediamine

The title compound was prepared in 97% yield from N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valine and the amine of Example 42 by the procedure described in Example 9 (solvent used: methylene chloride/dimethylformamide 3:1).
MS(DCI/Cl + /NH_3): 777(MNH^+_4, 66); 760(MH^+, 100); 703(20); 686(15); 660(15).

EXAMPLE 44

N^4-[N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-2.2-difluoro-6-methyl-N^1-(3-methyl-2R-phenylacetylaminobutanoyl)-3-oxo-1.4-heptanediamine

The title compound was prepared in 50% yield from the alcohol of Example 43 by the procedure described in Example 8.
MS: 775(MNH^+_4, 30); 758(MH^+, 100).

EXAMPLE 45

N^1-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N^4-[N-benzyloxycarbonyl)-L-phenylalanyl-L-n-valyl]-2.2-

difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared in 77% yield from the N-(benzyloxycarbonyl)-L-phenylalanyl-L-n-valine and the amine of Example 32 by the procedure described in Example 9.
Rf: 0.47 (silica gel; chloroform/methanol 92:8)
MS(DCI/Cl + /NH_3): 811(MNH^+_4, 25); 794(MH^+, 9); 703(100); 686(18); 660(5); 613(7).

EXAMPLE 46

N^1-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N^4-[N-benzyloxycarbonyl)-L-phenylalanyl-L-n-valyl]-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine

The title compound was prepared in 82% yield from the alcohol of Example 45 by the procedure described in Example 8.
Rf: 0.64 (silica gel: chloroform/methanol 92:8)
MS(DCI/Cl + /CH_4): 792(MH^+).

EXAMPLE 47

N^1-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N^4-[N-benzyloxycarbonyl)-N^{im}-tert-butoxycarbonyl-L-histidyl]-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine

The title compound was prepared in 60% yield from the alcohol of Example 33 by the procedure described in Example 8.
Rf: 0.44 (silica gel; ethyl acetate)
MS(DCI/Cl + /NH_3): 783(MH^+, 40); 683(66); 575(38); 457(100).

EXAMPLE 48

N^1-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N^4-[N-benzyloxycarbonyl)-L-histidyl]-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine

The title compound was prepared in 54% yield from the ketone of Example 47 by the procedure described in Example 40.
Rf: 0.19 (silica gel; chloroform/methanol 92:8)
MS(DCI/Cl + /NH_3): 683(MH^+, 100); 575(60).

EXAMPLE 49

N^1-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N^4-[[N-benzyloxycarbonyl)-3-(1-napthyl)alanyl]-N^{im}-tert-butoxycarbonyl-L-histidyl]-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine

The title compound was prepared in 50% yield from the alcohol of Example 35 by the procedure described in Example 8.
Rf: 0.36 (silica gel; ethyl acetate)
MS(DCI/Cl + NH_3): 980(MH^+, 2); 880(16); 772(100); 753(26); 732(90); 575(23); 498(100).

EXAMPLE 50

N^1-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N^4-[[N-benzyloxycarbonyl)-3-(1-naphthyl)alanyl]-L-histidyl]-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine

The title compound was prepared from the carbamate of Example 49 by the procedure described in Example 40.

EXAMPLE 51

N^1-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N^4-[N-(tert-butoxycarbonyl-L-phenylalanyl-N^{im}-(tert-butoxycarbonyl)-L-histidyl]-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared in 50% yield from (N-tert-butoxycarbonyl)-L-phenylalanine and the amine of Example 34 by the procedure described in Example 5.
Rf: 0.43 (silica gel: ethyl acetate).

EXAMPLE 52

N^1-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N^4-[N-(tert-butoxycarbonyl-L-phenylalanyl-N^{im}-(tert-butoxycarbonyl)-L-histidyl]-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine

The title compound was prepared in 53% yield from the alcohol of Example 51 by the procedure described in Example 8.
Rf: 0.57 (silica gel: ethyl acetate).
MS(DCI/Cl + iNH_3): 896.5(MH^+, 24); 796.4(76); 696.4(4); 649.4(100).

EXAMPLE 53

N^1-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N^4-[N-(tert-butoxycarbonyl)-L-phenylalanyl-L-histidyl]-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine

To a solution of N^1-(2-benzylaminocarbonyl-3-methylbutanoyl)-N^4-[N-(tert-butoxycarbonyl-L-phenylalanyl-N^{im}-(tert-butoxycarbonyl)-L-histidyl]-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine (0.179 g, 0.2 mmol) in methanol (3 mL) was added anhydrous potassium carbonate (0.063 g, 0.46 mmol). The mixture was stirred 1.5 hours at room temperature. Acetic acid (0.2 mL) was added and the mixture was evaporated to dryness, at reduced pressure. The residue was taken off in ethyl acetate. The organic solution was washed with 5% sodium bicarbonate, and dried over anhydrous magnesium sulphate. Filtration, removal of the solvent *in vacuo* and purification by flash chromatography yielded the title compound as a white solid.

EXAMPLE 54

N^1-(2-Benzylaminocarbonylpropanoyl)-N^4-(benzyloxycarbonyl)-2,2-difluoro-3-hydroxy-6-methyl-1,4-

heptanediamine

The title compound was prepared in 81% yield from 2-benzylaminocarbonylpropanoic acid and the amine of Example 4 by the procedure described in Example 9.
Rf: 0.48 (silica gel; ethyl acetate)
MS(DCI/Cl + /NH_3): 537(MNH^+_4, 96); 520(MH^+, 100); 420(10); 386(28); 242(37); 225(89).

EXAMPLE 55

N^1-(2-Benzylaminocarbonylpropanoyl)-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared in 87% yield from the carbamate of Example 54 by the procedure described in Example 6.

EXAMPLE 56

N^1-(2-Benzylaminocarbonylpropanoyl)-N^4-[N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared in 66% yield from N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valine and the amine of Example 55 by the procedure described in Example 5.
Rf: 0.40 (silica gel; chloroform/methanol 92:8)
MS(DCI/Cl + /NH_3): 749(MNH^+_4, 28); 732(MH^+, 82); 632(39); 282(96); 265(100).

Analysis calculated for $C_{38}H_{55}N_5O_7F_2$:	C%: 62.36;	H%: 7.57;	N%: 9.57.
Found:	C%: 62.13;	H%: 7.59;	N%: 9.34.

EXAMPLE 57

N^1-(2-Benzylaminocarbonylpropanoyl)-N^4-[N-(tert-butoxycarbonyl)-L-phenylallanyl-L-n-valyl]-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine

The title compound was prepared in 79% yield from the alcohol of Example 56 by the procedure described in Example 8.
Rf: 0.52 (silica gel; chloroform/methanol 92:8)
MS(DCI/Cl + /NH_3): 748(MNH^+_4, 16); 731(MH^+, 100).

Analysis calculated for $C_{38}H_{53}N_5O_7F_2$:	C%: 62.53;	H%: 7.32;	N%: 9.59.
Found:	C%: 62.10;	H%: 7.37;	N%: 9.53.

EXAMPLE 58

N^1-(2-Benzylaminocarbonylacetyl)-N^4-(benzyloxycarbonyl)-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared in 65% yield from 2-benzylaminocarbonylacetic acid and the amine of Example 4 by the procedure described in Example 9.
Rf: 0.32 (silica gel; ethyl acetate)
MS(DCI/Cl + /NH_3): 523(MNH^+_4, 100); 506(MH^+, 26).

Analysis calculated for $C_{26}H_{33}N_3O_5F_2$:	C%: 61.77;	H%: 6.58;	N%: 8.31.
Found:	C%: 61.50:	H%: 6.59;	N%: 8.23.

EXAMPLE 59

N^1-(2-Benzylaminocarbonylacetyl)-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared in 93% yield from the carbamate of Example 58 by the procedure described in Example 6.

EXAMPLE 60

N^1-(2-Benzylaminocarbonylacetyl)-N^4-[N-(tert-butyoxycarbonyl)-L-phenylalanyl-L-n-valyl]-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared in 33% yield from N-(tert-butoxycarbonyl-L-phenylalanyl-L-n-valine and the amine of Example 59 by the procedure described in Example 5.
Rf: 0.42 (silica gel; chloroform/methanol 92:8)
MS(DCI/Cl + /NH_3): 736(MNH^+_4, 58); 719(MH^+, 100).

EXAMPLE 61

N^1-(2-Benzylaminocarbonylacetyl)-N^4-[N-(tert-butyoxycarbonyl)L-phenylalanyl-L-n-valyl]-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine

The title compound was prepared in 46% yield from the alcohol of Example 60 by the procedure described in Example 8.
m.p.: 81 °C
Rf: 0.34 (silica gel; ethyl acetate)
MS(DCI/Cl + /NH_3): 716.5(MH^+, 100).

EXAMPLE 62

N^1-(2-Benzylaminocarbonylpropanoyl)-N^4-[N-(tert-butoxycarbonyl)-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

A mixture of 0.157 g, of N^1-(2-benzylaminocarbonylpropanoyl)-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine (Example 55) and ditertiobutyldicarbonate (0.088 g) in anhydrous tetrahydrofuran (5 mL) was stirred at room temperature for 15 hours. Removal of the solvent in vacuo and chromatography (silica gel; ethyl acetate:cyclohexane 3:7) yielded 0.140 g of the title compound (72% yield).
Rf: 0.50 (silica gel; ethyl acetate)
MS(DCI/Cl + /NH_3): 503(MNH^+_4, 60); 486(MH^+, 100).

EXAMPLE 63

N^1-(2-Benzylaminocarbonylpropanoyl)-N^4-(tert-butoxycarbonyl)-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine

The title compound was prepared in 63% yield from the alcohol of Example 62 by the procedure described in Example 8.
Rf: 0.60 (silica gel; ethyl acetate)
MS(DCI/Cl + /NH_3): 501(MNH^+_4, 100); 484(MH^+, 45).

EXAMPLE 64

N^1-(2-Benzylaminocarbonylpropanoyl)-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine, hydrochloride

A mixture of 0.085 g of ketone of Example 63 and a saturated solution of hydrogen chloride in diethyl ether (6 mL) was stirred at room temperature for 15 hours. A white precipitate formed during that time. The solid was filtered off, rinsed thoroughly with pentane and dried in high vacuo.
Rf: 0.46 (silica gel; AcOH/BuOH/H_2O, 2:6:2)
MS(DCI/Cl + /NH_3): 384(MH^+, 100); 344(74).

EXAMPLE 65

N^1-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N^4-(tert-butoxycarbonyl)-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared in 65% yield from the amine of Example 32 by the procedure described in Example 62.
Rf: 0.62 (silica gel; ethyl acetate)
MS(DCI/Cl + /NH_3): 531(MNH^+_4, 10); 514(MH^+, 100).

EXAMPLE 66

N^1-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N^4-(tert-butoxycarbonyl)-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine

The title compound was prepared in 79% yield from the alcohol of Example 65 by the procedure described in Example 8.
Rf: 0.75 (silica gel; ethyl acetate)
MS(DCI/Cl + /NH_3): 529(MNH^+_4, 70); 512(MH^+, 100), 489(14).

EXAMPLE 67

N^1-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N^4-(tert-butoxycarbonyl)-2,2-difluoro-6-methyl-3-oxo-1,4-heptanediamine, hydrochloride

The title compound was prepared in 94% yield from the ketone of Example 66 by the procedure described in Example 64.
m.p.: 110° C (decomposition)
Rf: 0.65 (silica gel; AcOH/BuOH/H_2O, 2:6:2)
MS(DCI/Cl + /NH_3): 412(MH^+, 75); 372(45), 103(100)

Analysis calculated for $C_{21}H_{32}N_3O_3F_2Cl,H_2O$:	C%: 54.13;	H%: 7.35;	N%: 9.02.
Found:	C%: 54.55;	H%: 7.37;	N%: 8.76.

EXAMPLE 68

N^4-Benzyloxycarbonyl-2,2-difluoro-3-hydroxy-6-methyl-N^1-(2R-phenylacetylaminopropanoyl)-1,4-heptanediamine

The title compound was prepared in 67% yield from 2R-phenylacetylaminopropanoic acid and the amine of Example 4 by the procedure described in Example 9.
m.p.: 146° C
MS(DCI/Cl + /NH_3): 537(MNH_4^+, 100); 520(MH^+, 42), 386(20); 153(55)

Analysis calculated for $C_{27}H_{35}N_3O_5F_2$:	C%: 62.41;	H%: 6.79;	N%: 8.09.
Found:	C%: 62.34;	H%: 6.83;	N%: 7.93.

EXAMPLE 69

2,2-Difluoro-3-hydroxy-6-methyl-N^1-(2R-phenylacetylaminopropanoyl)-1,4-heptanediamine

The title compound was prepared in 95% yield from the carbamate of Example 68 by the procedure described in Example 6.

EXAMPLE 70

N^4-(tert-Butoxycarbonyl)-2,2-difluoro-3-hydroxy-6-methyl-N^1-(2R-phenylacetylaminopropanoyl)-1,4-heptanediamine

The title compound was prepared in 78% yield from the amine of Example 69 by the procedure described in Example 62.

Rf: 0.50 (silica gel; ethyl acetate)
MS(DCI/Cl + /NH_3): 503(MNH^+_4, 93); 486(MH^+, 100).

EXAMPLE 71

N^4-(tert-Butoxycarbonyl)-2,2-difluoro-6-methyl-N^1-(2R-phenylacetylaminopropanoyl)-3-oxo-1,4-heptanediamine

The title compound was prepared in 96% yield from the alcohol of Example 70 by the procedure described in Example 8.
Rf: 0.60 (silica gel; ethyl acetate)
MS(DCI/Cl + /NH_3): 501(MNH^+_4, 55); 484(MH^+, 74); 466(18); 445(44); 428(100).

EXAMPLE 72

2,2-Difluoro-6-methyl-N^1-(2R-phenylacetylaminopropanoyl)-3-oxo-1,4-heptanediamine, hydrochloride

The title compound was prepared in 91% yield from the ketone of Example 71 by the procedure described in Example 64.
m.p.: 110° C (decomposition)
Rf: 0.59 (silica gel; AcOH/BuOH/H_2O, 2:6:2)
MS(DCI/Cl + /NH_3): 384(MH^+, 100); 344(34); 153(85); 103(85).

EXAMPLE 73

N^4-Benzyloxycarbonyl-2,2-difluoro-3-hydroxy-6-methyl-N^1-(3-methylbutanoyl)-1,4-heptanediamine

The title compound was prepared in 86% yield from isovaleric acid and the amine of Example 4 by the procedure described in Example 5.
Rf: 0.33 (silica gel; ethyl acetate/cyclohexane 1:1)
MS(DCI/Cl + /NH_3): 432(MNH^+_4, 100); 415(MH^+, 57); 281(70).

EXAMPLE 74

2,2-Difluoro-3-hydroxy-6-methyl-N^1-(3-methylbutanoyl)-1,4-heptanediamine

The title compound was prepared in 89% yield from the carbamate of Example 73 by the procedure described in Example 6.

EXAMPLE 75

N^4-[N-(tert-Butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-2,2-difluoro-3-hydroxy-6-methyl-N^1-(3-methylbutanoyl)-1,4-heptanediamine

The title compound was prepared in 82% yield from N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valine and the amine of Example 74 by the procedure described in Example 9.
Rf: 0.41 (silica gel; chloroform/methanol 92:8)
MS(DCI/Cl + /NH_3): 644(MNH^+_4, 61); 627(MH^+, 100).

EXAMPLE 76

N^4-[N-(tert-Butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-2,2-difluoro-6-methyl-N^1-(3-methylbutanoyl)-3-oxo-1,4-heptanediamine

The title compound was prepared in 60% yield from the alcohol of Example 75 by the procedure described in Example 8.
Rf: 0.49 (silica gel; chloroform/methanol 92:8)
MS(DCI/Cl + /NH_3): 643(MNH^+_4, 100); 625(MH^+, 35).

Analysis calculated for: $C_{32}H_{50}N_4O_6F_2$:	C%: 61.52;	H%: 8.07;	N%: 8.97;
Found:	C%: 61.56;	H%: 8.35;	N%: 8.81.

EXAMPLE 77

N^4-Benzyloxycarbonyl-2,2-difluoro-3-hydroxy-5-phenyl-1,4-pentanediamine

The trifluoroacetic acid salt of the title compound was prepared in quantitative yield from the carbamate of Example 15 by the procedure described in Example 4. An ethereal solution of this TFA salt was washed with saturated sodium bicarbonate (3 times) and dried over anhydrous magnesium sulphate. Filtration and removal of the solvent *in vacuo* yielded the title compound in 88% yield as a white solid.
MS(DCI/Cl + /NH_3): 382(MNH^+_4, 3); 365(MH^+, 100).

EXAMPLE 78

N^1-Acetyl-N^4-benzyloxycarbonyl-2,2-difluoro-3-hydroxy-5-phenyl-1,4-pentanediamine

The title compound was prepared in 70% yield from acetic anhydride and the amine of Example 77 by the procedure described in Example 17.
Rf: 0.39 (silica gel; ethyl acetate)
MS(DCI/Cl + /NH_3): 424(MNH^+_4, 100); 407(MH^+, 23); 273(62).

EXAMPLE 79

N^1-Acetyl-2,2-difluoro-3-hydroxy-5-phenyl-1,4-pentanediamine

The title compound was prepared in 84% yield from the carbamate of Example 78 by the procedure described in Example 6.

EXAMPLE 80

N^1-Acetyl-N^4-(N-acetyl-L-Leucyl)-2,2-difluoro-3-hydroxy-5-phenyl-1,4-pentanediamine

The title compound was prepared in 72% yield from N-acetyl-L-leucine and the amine of Example 79 by the procedure described in Example 9.
Rf: 0.17 (silica gel; chloroform/methanol 92:8)
MS(DCI/Cl + /NH_3): 445(MNH^+_4, 100); 428(MH^+, 54).

Analysis calculated for: $C_{21}H_{31}N_3O_4F_2$:	C%: 59.00;	H%: 7.31;	N%: 9.83.
Found:	C%: 58.98;	H%: 7.24;	N%: 9.42.

EXAMPLE 81

N^1-Acetyl-N^4-(N-acetyl-L-Leucyl)-2,2-difluoro-3-oxo-5-phenyl-1,4-pentanediamine

The title compound was prepared in 73% yield from the alcohol of Example 80 by the procedure described in Example 8.
Rf: 0.11 (silica gel; chloroform/methanol 92:8)
MS(DCI/Cl + /NH_3): 443(MNH^+_4, 100); 426(MH^+, 23).

Analysis calculated for: $C_{21}H_{29}N_3O_4F_2$:	C%: 59.28;	H%: 6.87;	N%: 9.88.
Found:	C%: 59.51;	H%: 7.02;	N%: 9.65.

EXAMPLE 82

N^4-Benzyloxycarbonyl-2,2-difluoro-3-hydroxy-5-methyl-1,4-hexanediamine, trifluoroacetate

The title compound was prepared in 66% yield from the carbamate of Example 23 by the procedure described in Example 77.

EXAMPLE 83

N^1-Acetyl-N^4-benzyloxycarbonyl-2,2-difluoro-3-hydroxy-5-methyl-1,4-hexanediamine

The title compound was prepared in 83% yield from the amine of Example 82 and acetic anhydride by the procedure described in Example 17.

EXAMPLE 84

N^1-Acetyl-2,2-difluoro-3-hydroxy-5-methyl-1,4-hexanediamine

The title compound was prepared in 89% yield from the carbamate of Example 83 by the procedure described in Example 6.

EXAMPLE 85

N^1-Acetyl-2,2-difluoro-3-hydroxy-N^4-(methoxysuccinyl-L-alanyl-L-alanyl-L-prolyl)-5-methyl-1,4-hexanediamine

The title compound was prepared in 43% yield from methoxysuccinyl-L-alanyl-L-alanyl-L-proline and the amine of Example 84 by the procedure described in Example 5.
Rf: 0.19 (silica gel; chloroform/methanol 92:8)
MS(DCI/Cl + /NH_3): 596(MH^+, 23); 563(100); 546(41).

EXAMPLE 86

N^1-Acetyl-2,2-difluoro-N^4-(methoxysuccinyl-L-alanyl-L-alanyl-L-prolyl)-5-methyl-3-oxo-1,4-hexanediamine

The title compound was prepared in 60% yield from the carbamate of Example 85 by the procedure described in Example 8.
Rf: 0.23(silica gel; chloroform/methanol 92:8)
MS(DCI/Cl + /NH_3): 593(MNH_4^+, 100); 576(MH^+, 52).

Analysis calculated for: $C_{25}H_{39}N_5O_8F_2$:	C%: 52.17;	H%: 6.83;	N%: 12.17.
Found:	C%: 52.54;	H%: 6.95;	N%: 11.58.

EXAMPLE 87

N^4-Benzyloxycarbonyl-N^1-(2-methylpropyloxycarbonyl)-2,2-difluoro-3-hydroxy-6-methyl-1,4-heptanediamine

The title compound was prepared in 89% yield from isobutylchloroformate and the amine of Example 4 by the procedure described in Example 17.
Rf: 0.45 (silica gel; ethyl acetate/cyclohexane 1:1)
MS(DCI/Cl + /NH_3): 448(MNH_4^+, 100); 431(MH^+, 28); 340(15); 297(57).

EXAMPLE 88

2,2-Difluoro-3-hydroxy-6-methyl-N^1-(2-methylpropyloxycarbonyl)-1,4-heptanediamine

The title compound was prepared in 93% yield from the carbamate of Example 87 by the procedure described in Example 6.

EXAMPLE 89

N^4-[N-(tert-Butoxycarbonyl)-L_1-phenylalanyl-L-n-valyl]-2,2-difluoro-3-hydroxy-6-methyl-N^1-(2-methylpropyloxycarbonyl)-1,4-heptanediamine

The title compound was prepared in 62% yield from N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valine and the amine of Example 88 by the procedure described in Example 5.
Rf: 0.60 (silica gel; chloroform/methanol 92:8)
MS(DCI/CI + /NH_3): 660(MNH^+_4, 30); 643(MH^+, 100).

EXAMPLE 90

N^4-[N-tert-Butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-2,2-difluoro-6-methyl-N^1-(2-methylpropyloxycarbonyl)-3-oxo-1,4-heptanediamine

The title compound was prepared in 84% yield from the alcohol of Example 89 by the procedure described in Example 8.
m.p.: 131 °C
Rf: 0.44 (silica gel; ethyl acetate/cyclohexane 1:1)
MS(DCI/CI + /NH_3): 658(MNH^+_4, 100); 641(MH^+, 98).

Analysis calculated for: $C_{32}H_{50}N_4O_7F_2$:	C%: 59.98;	H%: 7.86;	N%: 8.74.
Found:	C%: 60.40;	H%: 8.11;	N%: 8.39.

EXAMPLE 91

N^4-Benzoyl-N^1-(2-benzyloxycarbonylacetyl)-2,2-difluoro-3-hydroxy-5-phenyl-1,4-heptanediamine

The title compound was prepared in 42% yield from 2-benzyloxycarbonylacetic acid and the amine of Example 18 by the procedure described in Example 9.
Rf: 0.17 (silica gel; ethyl acetate/cyclohexane 1:1)
MS(CI/NH_3): 511(MH^+, 100).

EXAMPLE 92

N^4-Benzoyl-N^1-(2-benzyloxycarbonylacetyl)-2,2-difluoro-3-oxo-5-phenyl-1,4-pentanediamine

The title compound was prepared in 50% yield from the alcohol of Example 91 by the procedure described in Example 8.

EXAMPLE 93

N^4-Benzoyl-N^1-(2-carboxyacetyl)-2,2-difluoro-3-oxo-5-phenyl-1,4-pentanediamine

The title compound was prepared in quantitative yield from the ester of example 92 by the procedure described in Example 6.

EXAMPLE 94

N-Benzyloxycarbonyl-3-cyclohexylalanine

To a solution of 3-cyclohexylalanine, hydrochloride (4.75 g, 22.8 mmol) in 2N sodium hydroxide (11.4 mL) were added at 0 °C, simultaneously, a solution of benzylchloroformate (3.2 mL, 36 mmol) in tetrahydrofuran (10 mL) and 2N sodium hydroxide (11.4 mL). (The pH of the mixture was maintained around 9-10 by addition of 2N sodium hydroxide.) The mixture was stirred for 1.5 hours. The solution was washed with diethyl ether (3 x 20 mL). The aqueous phase was acidified to pH 2 with 3N aqueous hydrochloric acid and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over anhydrous magnesium sulphate. Filtration and removal of the solvent *in vacuo* left 4.80 g of the expected product (yellow oil, 69% yield).
Rf: 0.75 (silica gel, AcOH/BuOH/H_2O 2:6:2).

EXAMPLE 95

2-Benzyloxycarbonylamino-3-cyclohexyl-N,O-dimethylpropanehydroxamate

To a solution of N-benzyloxycarbonyl-3-cyclohexylalanine (4.60 g, 15 mmol) in anhydrous methylene chloride (60 mL) were added, at 0 °C, dicyclohexylcarbodiimide (3.09 g, 15 mmol) and 1-hydroxybenzotriazolehydrate (2.29 g, 15 mmol). After stirring for 0.25 hours at 0 °C, N,O,-dimethylhydroxylamine hydrochloride (1.46 g, 15 mmol) and N-methylmorpholine (1.51 g, 15 mmol) were added to the mixture. The mixture was stirred for 20 hours while the temperature was allowed to rise to room temperature. The precipitate was filtered off. The solvent was removed *in vacuo* and the mixture was purified by chromatography (silica gel; ethyl acetate/cyclohexane 2:8) yielding 3.60 g of the expected hydroxamate (69% yield).
Rf: 0.38 (silica gel; ethyl acetate/cyclohexane 1:1, UV, I_2).

EXAMPLE 96

N-Benzyloxycarbonyl-3-cyclohexylalaninal

A mixture of 2-benzyloxycarbonylamino-3-cyclohexyl-N,O-dimethylpropanehydroxamate (3.58 g, 10.3 mmol), and lithium aluminiumhydride (0.44 g, 11.6 mmol) in anhydrous diethyl ether (100 mL) was stirred at 0 °C for 1 hour. 1M potassium hydrogenosulphate (25 mL) was added. The mixture was stirred for 0.5 hour and extracted with diethyl ether (2 x 25 mL).

The combined organic layers were washed with 2N HCl (3 x 20 mL), water (1 x 20 mL), a saturated solution of sodium bicarbonate (1 x 20 mL), brine (20 mL) and dried over anhydrous magnesium sulphate. Filtration and removal of the solvent *in vacuo* left 2.52 g of the expected aldehyde (85%, yellowish oil) used in the next step without further purification.

EXAMPLE 97

4-Benzyloxycarbonylamino-5-cyclohexyl-2,2-difluoro-3-hydroxypentanoic acid, ethyl ester

The title compound was prepared in 37% yield from N-benzyloxycarbonyl-3-cyclohexylalaninal, ethyl bromodifluoroacetate and zinc by the procedure described in Example 1.
Rf: 0.57 (silica gel; ethyl acetate/cyclohexane 1:1).

EXAMPLE 98

4-Benzyloxycarbonylamino-5-cyclohexyl-2,2-difluoro-3-hydroxypentanamide

The title compound was prepared in 97% yield from the ester of Example 97 by the procedure described in Example 2.
Rf: 0.53 (silica gel; ethyl acetate)
MS(DCI/Cl + /NH_3): 402(MNH^+_4, 86); 385(MH^+, 13); 294(23); 169(40); 126(100).

EXAMPLE 99

N^4-Benzyloxycarbonyl-N^1-(tert-butoxycarbonyl)-5-cyclohexyl-2,2-difluoro-3-hydroxy-1,4-pentanediamine

The title compound was prepared in 51% yield from the amide of Example 98 by the procedure described in Example 3.
Rf: 0.59 (silica gel; ethyl acetate/cyclohexane 1:1).

EXAMPLE 100

N^4-Benzyloxycarbonyl-5-cyclohexyl-2,2-difluoro-3-hydroxy-1,4-pentanediamine

The title compound was prepared in 60% yield from the carbamate of Example 99 by the procedure described in Example 77.

EXAMPLE 101

N^1-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N^4-benzyloxycarbonyl-5-cyclohexyl-2,2-difluoro-3-hydroxy-1,4-pentanediamine

The title compound was prepared in 58% yield from 2-benzylaminocarbonyl-3-methylbutanoic acid and the amine of Example 100 by the procedure described in Example 9.
Rf: 0.60 (silica gel; ethyl acetate)

Analysis calculated for $C_{32}H_{43}N_3O_5F_2$			
found	C%: 65.40; C%: 65.01;	H%: 7.37; H%: 7.42;	N%: 7.15 N%: 7.06.

EXAMPLE 102

N^1-(2-Benzylaminocarbonyl-3-methylbutanoyl)-5-cyclohexyl-2,2-difluoro-3-hydroxy-1,4-pentanediamine

The title compound was prepared in 82% yield from the carbamate of Example 101 by the procedure described in Example 6.

EXAMPLE 103

N^1-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N^4-[N-tert-butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-5-cyclohexyl-2,2-difluoro-3-hydroxy-1,4-pentanediamine

The title compound was prepared in 60% yield from N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valine and the amine of Example 102 by the procedure described in Example 5.
Rf: 0.46 (silica gel; chloroform/methanol 92:8)
MS(DCI/Cl + /NH_3): 817(MNH^+_4, 10); 800(MH^+, 100); 700(60).

Analysis calculated for $C_{43}H_{63}N_5O_7F_2$			
found	C%: 64.56; C%: 64.47;	H%: 7.94; H%: 8.13;	N%: 8.75 N%: 8.58.

EXAMPLE 104

N^1-(2-Benzylaminocarbonyl-3-methylbutanoyl)-N^4-[N-tert-butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-5-cyclohexyl-2,2-difluoro-3-oxo-1,4-pentanediamine

The title compound was prepared in 64% yield from the alcohol of Example 103 by the procedure described in Example 8.
Rf: 0.53 (silica gel; chloroform/methanol 92:8)
MS(DCI/Cl + /NH_3): 815(MNH^+_4, 10); 798(MH^+, 100).

EXAMPLE 105

Ethyl 4-benzyloxycarbonylamino-2,2-difluoro-3-hydroxy butanoate

The title compound was prepared in 33% yield from N-benzyloxycarbonylglycinal, ethyl bromodifluoroacetate and zinc by the procedure described in Example 1.
Rf: 0.45 (silica gel; ethyl acetate/cyclohexane 1:1).

EXAMPLE 106

4-Benzyloxycarbonylamino-2,2-difluoro-3-hydroxy butanamide

The title compound was prepared in 95% yield from the ester of Example 105 by the procedure described in Example 2.
Rf: 0.49 (silica gel; ethyl acetate/cyclohexane 1:1).

EXAMPLE 107

N^4-Benzyloxycarbonyl-N^1-(tert-butoxycarbonyl)-2,2-difluoro-3-hydroxy-1,4-butanediamine

The title compound was prepared in 48% yield from the amide of Example 106 by the procedure described in Example 3.
Rf: 0.42 (silica gel; ethyl acetate/cyclohexane 1:1)
MS(DCI/Cl + /NH_3): 392(MNH^+_4, 59); 375(MH^+, 20); 258(15); 241(100).

EXAMPLE 108

Ethyl benzyloxycarbonylamino-2,2-difluoro-3-hydroxy pentanoate

The title compound was prepared in 50% yield from N-benzyloxycarbonylalaninal, ethyl bromodifluoroacetate and zinc by the procedure described in Example 1.
Rf: 0.49 (silica gel; ethyl acetate/cyclohexane 1:1).

EXAMPLE 109

4-Benzyloxycarbonylamino-2,2-difluoro-3-hydroxy pentanamide

The title compound was prepared in 90% yield from the ester of Example 108 by the procedure described in Example 2.
Rf: 0.50 (silica gel; ethyl acetate/cyclohexane 1:1)
MS(DCI/Cl + /NH_3): 320(MNH^+_4, 100); 303(MH^+, 13); 212(19); 169(100).

EXAMPLE 110

N^4-Benzyloxycarbonyl-N^1-(tert-butoxycarbonyl)-2,2-difluoro-3-hydroxy-1,4-pentanediamine

The title compound was prepared in 53% yield from the amine of Example 109 by the procedure described in Example 3.
Rf: 0.47 (silica gel; ethyl acetate/cyclohexane 1:1)
MS(DCI/Cl + /NH_3): 406(MNH^+_4, 94); 389(MH^+, 23); 298(20); 255(100).

EXAMPLE 111

N^4-Benzyloxycarbonyl-5-cyclohexyl-2,2-difluoro-3-hydroxy-N^1-(3-methylbutanoyl)-1,4-pentanediamine

The title compound was prepared in 60% yield from isovaleric acid and the amine of Example 100 by the procedure described in Example 5.
Rf: 0.34 (silica gel; ethyl acetate/cyclohexane 1:1)
MS(DCI/Cl + /NH_3): 472(MNH^+_4, 63); 455(MH^+, 34); 321(100).

EXAMPLE 112

5-Cyclohexyl-2,2-difluoro-3-hydroxy-N^1-(3-methylbutanoyl)-1,4-pentanediamine

The title compound was prepared in 69% yield from the carbamate of Example 111 by the procedure described in Example 6.

EXAMPLE 113

N^4-[N-(tert-Butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-5-cyclohexyl-2,2-difluoro-3-hydroxy-N^1-(3-methylbutanoyl)-1,4-pentanediamine

The title compound was prepared in 78% yield from N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valine and the amine of Example 112 by the procedure described in Example 5.
Rf: 0.18 (silica gel; ethyl acetate/cyclohexane 1:1)
MS(DCI/Cl + /NH_3): 684(MNH^+_4, 29); 667(MH^+, 100).

EXAMPLE 114

N^4-[N-(tert-Butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-5-cyclohexyl-2,2-difluoro-N^1-(3-methylbutanoyl)-3-oxo-1,4-pentanediamine

The title compound was prepared in 74% yield from the alcohol of Example 113 by the procedure described in Example 8.
Rf: 0.41 (silica gel; ethyl acetate/cyclohexane 1:1)
MS(DCI/Cl + /NH_3): 682(MNH^+_4, 5); 665(MH^+, 18); 364(100)

Analysis calculated for $C_{35}H_{54}N_4O_6F_2$			
found	C%: 63.23; C%: 62.78;	H%: 8.19; H%: 8.27;	N%: 8.43 N%: 8.12.

EXAMPLE 115

N^4-Benzyloxycarbonyl-2,2-difluoro-3-hydroxy-6-methyl-N^1-[2-(2-methylpropyl)-5-phenylpentanoyl]-1,4-heptanediamine

The title compound was prepared in 54% yield from 2-(2-methylpropyl)-5-phenylpentanoyl chloride and the amine of Example 4 by the procedure described in Example 17.
MS(DCI/Cl + /NH_3): 564(MNH^+_4, 40); 547(MH^+, 30); 413(100).

EXAMPLE 116

2,2-Difluoro-3-hydroxy-6-methyl-N^1-[2-(2-methylpropyl)-5-phenylpentanoyl]-1,4-heptanediamine

The title compound was prepared in 87% yield from the carbamate of Example 115 by the procedure described in Example 6.
MS(DCI/Cl + /NH_3): 413(MH^+).

EXAMPLE 117

N^4-[N-(tert-Butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-2,2-difluoro-3-hydroxy-6-methyl-N^1-[2-(2-methylpropyl)-5-phenylpentanoyl]-1,4-heptanediamine

The title compound was prepared in 26% yield from N-(tert-butoxycarbonyl)-L-phenylalanyl-L-n-valine and the amine of Example 116 by the procedure described in Example 5.
Rf: 0.61 (silica gel; chloroform/methanol 92:8)
MS(DCI/Cl + /NH_3): 776(MNH^+_4, 65); 759(MH^+, 89); 282(85); 265(100).

EXAMPLE 118

N^4-[N-(tert-Butoxycarbonyl)-L-phenylalanyl-L-n-valyl]-2,2-difluoro-6-methyl-N^1-[2-(2-methylpropyl)-5-phenylpentanoyl]-3-oxo-1,4-heptanediamine

The title compound was prepared in 62% yield from the alcohol of Example 117 by the procedure described in Example 8.
Rf: 0.50 (silica gel; ethyl acetate/cyclohexane 1:1)

Analysis calculated for $C_{42}H_{62}N_4O_6F_2$:	C%: 66.64;	H%: 8.25;	N%: 7.40.
Found:	C%: 66.62;	H%: 8.52;	N%: 6.86.

EXAMPLE 119

N-Benzyloxycarbonyl-4-nitrophenylalanine, methyl ester

To a mixture of N-benzyloxycarbonyl-4-nitrophenylalanine (0.3 g, 0.9 mmol) in ethyl acetate (10 mL) was added at 0 °C a 0.5 M solution of diazomethane in diethyl ether until persistence of a yellow color. The mixture was stirred for 0.5 hour at 0 °C. Acetic acid was added to destroy the excess of diazomethane (disappearance of the yellow color). Removal of the solvent *in vacuo* and purification of the crude product by chromatography (silica gel; ethyl acetate/cyclohexane 2:8) yielded 0.219 g of the title compound (70%

yield).
Rf: 0.38 (silica gel; ethyl acetate/cyclohexane 1:1).

EXAMPLE 120

N-Benzyloxycarbonyl-4-nitrophenylalaninal

To a suspension of N-benzyloxycarbonyl-4-nitrophenylalanine, methyl ester (2.55 g, 7.1 mmol) in a mixture of toluene and diethyl ether (60 mL, 5:1), was added dropwise at -78 °C, under nitrogen, a solution of DIBAL in toluene (1M, 14.3 mL). The mixture was stirred at -78 °C for 30 min. Methanol (5 mL) and a saturated aqueous solution of Rochelle's salt (30 mL) were added and the mixture was extracted with diethyl ether (2 x 100 mL). The combined organic layers were dried over anhydrous magnesium sulphate. Filtration, removal of the solvent *in vacuo*, and chromatography (silica gel, ethyl acetate/n-hexane 2:8) yielded 1.709 g of the title compound (73% yield).
Rf: 0.18 (silica gel; ethyl acetate/cyclohexane 1:1).

EXAMPLE 121

4-Benzyloxycarbonylamino-2,2-difluoro-3-hydroxy-5-(4-nitrophenyl)pentanoic acid, ethyl ester

The title compound was prepared in 30% yield from the aldehyde of Example 120, ethyl bromodifluoroacetate and zinc, by the procedure described in Example 1.
MS(DCI/Cl + /NH_3): 470(MNH_4^+, 100); 453(MH^+, 5).

EXAMPLE 122

4-Benzyloxycarbonylamino-2,2-difluoro-3-hydroxy-5-(4-nitrophenyl)pentanamide

The title compound was prepared in 70% yield from the ester of Example 121 by the procedure described in Example 2.

EXAMPLE 123

N^4-Benzyloxycarbonyl-N^1-tert-butoxycarbonyl-2,2-difluoro-3-hydroxy-5-(4-nitrophenyl)-1,4-pentanediamine

The title compound was prepared from the amide of Example 122 by the procedure described in Example 3.

EXAMPLE 124

N^4-Benzyloxycarbonyl-2,2-difluoro-3-hydroxy-5-(4-nitrophenyl)-1,4-pentanediamine

The title compound was prepared from the carbamate of Example 123 by the procedure described in

Example 77.

EXAMPLE 125

N^1-Acetyl-N^4-benzyloxycarbonyl-2,2-difluoro-3-hydroxy-5-(4-nitrophenyl)-1,4-pentanediamine

The title compound was prepared from the amine of Example 124 and acetic anhydride by the procedure described in Example 17.

EXAMPLE 126

N^1-Acetyl-N^4-benzyloxycarbonyl-2,2-difluoro-3-hydroxy-5-(4-aminophenyl)-1,4-pentanediamine

A mixture of N^1-acetyl-N^4-benzyloxycarbonyl-2,2-difluoro-3-hydroxy-5-(4-nitrophenyl)-1,4-pentanediamine (0.451 g, 1 mmol) and tin dichloride, 2 H_2O (1.128 g, 5 mmol) in absolute ethanol (5 mL) was heated at reflux under nitrogen for 1 hour. The mixture was allowed to cool to room temperature and was poured into ice. The pH was made slightly basic (pH 7-8) by addition of aqueous sodium bicarbonate, and the mixture was extracted with ethyl acetate. The organic phase was washed with brine, treated with charcoal and dried over anhydrous magnesium sulphate. Filtration and removal of the solvent *in vacuo* yielded the title compound.

EXAMPLE 127

N^1-Acetyl-N^4-benzyloxycarbonyl-5-(4-tert-butoxycarbonylaminophenyl)-2,2-difluoro-3-hydroxy-1,4-pentanediamine

A solution of amine of Example 126 (0.214 g, 0.5 mmol) and di-tert-butyldicarbonate (0.131 g, 0.6 mmol) in tetrahydrofuran (10 mL) was heated at reflux for 15 hours, under nitrogen. Removal of the solvent in vacuo and chromatography (silica gel, ethyl acetate/cyclohexane 1:1) yielded the expected carbamate.

EXAMPLE 128

N^1-Acetyl-5-(4-butoxycarbonylaminophenyl)-2,2-difluoro-3-hydroxy-1,4-pentanediamine

The title compound was prepared from the carbamate of Example 127 by the procedure described in Example 6.

EXAMPLE 129

N^1-Acetyl-N^4-benzoyl-5-(4-tert-butoxycarbonylaminophenyl)-2,2-difluoro-3-hydroxy-1,4-pentanediamine

The title compound was prepared from the amine of Example 128 and benzoyl chloride by the procedure described in Example 17.

EXAMPLE 130

N^1-Acetyl-N^4-benzoyl-5-(4-tert-butoxycarbonylaminophenyl)-2,2-difluoro-3-oxo-1,4-pentanediamine

The title compound was prepared from the alcohol of Example 129 by the procedure described in Example 8.

EXAMPLE 131

N^1-Acetyl-5-(4-aminophenyl)-N^4-benzoyl-2,2-difluoro-3-oxo-1,4-pentanediamine

The title compound was prepared from the carbamate of Example 130 by the procedure described in Example 77.

EXAMPLE 132

N^1-Acetyl-N^4-benzoyl-5-[4-[N′,N″-bis(tert-butoxycarbonyl)-guanidino]phenyl]-2,2-difluoro-3-oxo-1,4-pentanediamine

A mixture of N^1-acetyl-5-(4-aminophenyl)-N^4-benzoyl-2,2-difluoro-3-oxo-1,4-pentanediamine (0.195 g, 0.5 mmol) and N,N′-bis(tert-butoxycarbonyl)-S-methylisothiourea (0.174 g, 0.6 mmol) in tetrahydrofuran (10 mL) was heated at 55 °C for 15 hours. Removal of the solvent *in vacuo* left a solid residue. The residue was treated with 5% sodium bicarbonate and extracted with chloroform (2 x 20 mL). The combined organic layers were washed with water and the product was purified by chromatography (silica gel, chloroform/methanol 2:98) to yield the title compound.

EXAMPLE 133

N^1-Acetyl-N^4-benzoyl-5-(guanidinophenyl)-2,2-difluoro-3-oxo-1,4-pentanediamine, bistrifluoroacetate

The title compound was prepared from the carbamate of Example 132 by the procedure described in Example 4.

EXAMPLE 134

ε-N-Benzyloxycarbonyl-α-N-4-nitrobenzyloxycarbonyllysine

To a solution of ε-N-benzyloxycarbonyllysine (2.80 g, 10 mmol) in a mixture of tetrahydrofuran (25 mL) and 0.5N sodium hydroxide (50 mL) was added dropwise, at 0 °C, a solution of 4-nitro-benzylchloroformate (2.685 g) in tetrahydrofuran (25 mL). After completion of the addition, the temperature was allowed to rise to room temperature, and the mixture was stirred for 2 hours at that temperature. The mixture was diluted with water and washed with diethyl ether (2 x 50 mL). The aqueous phase was acidified (pH 2) and extracted with chloroform (3 x 80 mL). The combined organic extracts were dried over anhydrous magnesium sulphate. Filtration and removal of the solvent *in vacuo* yielded 4.042 g of the title compound (88% yield).

Rf: 0.85 (silica gel; AcOH/BuOH/H_2O 2:6:2).
MS(DCI/Cl + /NH_3): 477(MNH^+_4, 80); 460(MH^+, 15); 324(18); 281(85); 250(20); 237(52); 235(100); 218(45).

EXAMPLE 135

ε-N-Benzyloxycarbonyl-α-N-4-nitrobenzyloxycarbonyllysine, methyl ester

The title compound was prepared in 90% yield from the acid of Example 134 by the procedure described in Example 119.
m.p.: 74-75° c
Rf: 0.19 (silica gel; ethyl acetate/cyclohexane 1:1)
MS(DCI/Cl + /NH_3): 491(MNH^+_4, 44); 474(MH^+, 7); 295(100).

EXAMPLE 136

ε-N-Benzyloxycarbonyl-α-N-4-nitrobenzyloxycarbonyllysinal

The title compound was prepared in 76% yield from the ester of Example 135 by the procedure described in Example 120.
Rf: 0.11 (silica gel; ethyl acetate/cyclohexane 1:1).

EXAMPLE 137

8-Benzyloxycarbonylamino-2,2-difluoro-3-hydroxy-4-(4-nitrobenzyloxycarbonylamino)-octanoic acid, ethyl ester

The title compound was prepared in 30% yield from the aldehyde of Example 136 by the procedure described in Example 1.
Rf: 0.56 (silica gel; ethyl acetate)
MS(DCI/Cl + /NH_3): 585(MNH^+_4, 100); 568(MH^+, 19); 450(23); 389(65); 255(45); 235(63).

EXAMPLE 138

8-Benzyloxycarbonylamino-2,2-difluoro-3-hydroxy-4-(4-nitrobenzyloxycarbonylamino)-octanamide

The title compound was prepared in quantitative yield from the ester of Example 137 by the procedure described in Example 2.
Rf: 0.25 (silica gel; ethyl acetate)
MS(DCI/Cl + /NH_3): 556(MNH^+_4, 54); 539(MH^+, 4); 421(13); 403(46); 360(41); 139(38); 106(100).

EXAMPLE 139

N^3-Benzyloxycarbonyl-N^1-(tert-butoxycarbonyl)-2,2-difluoro-3-hydroxy-N^4-(4-nitrobenzyloxycarbonyl)-1,4,8-

octanetriamine

The title compound was prepared in 32% yield from the amide of Example 138 by the procedure described in Example 3.
MS(DCI/Cl + /NH_3): 642(MNH_4^+, 100); 625(MH^+, 10); 525(20); 507(20); 490(8); 446(28); 312(45).

EXAMPLE 140

N^8-Benzyloxycarbonyl-2,2-difluoro-3-hydroxy-N^4-(4-nitrobenzyloxycarbonyl)-1,4,8-octanetriamine

The title compound was prepared from the carbamate of Example 139 by the procedure described in Example 77.

EXAMPLE 141

N^1-Acetyl-N^8-benzyloxycarbonyl-2,2-difluoro-3-hydroxy-N^4-(4-nitrobenzyloxycarbonyl)-1,4,8-octanetriamine

The title compound was prepared from the amine of Example 140 by the procedure described in Example 17.

EXAMPLE 142

N^1-Acetyl-N^8-benzyloxycarbonyl-2,2-difluoro-3-hydroxy-1,4,8-octanetriamine

A mixture of N^1-acetyl-N^8-benzyloxycarbonyl-2,2-difluoro-3-hydroxy-N^4-(4-nitrobenzyloxycarbonyl)-1,4,8-octanetriamine (0.273 g, 0.5 mmol) and tin dichloride, 2 H_2O (0.564 g, 2.5 mmol) in absolute ethanol (5 mL) was heated at reflux under nitrogen for 1 hour. The mixture was allowed to cool to room temperature and was poured into ice. The pH was made basic (9-10) and the mixture was extracted with ethyl acetate. The organic phase was washed with brine, treated with charcoal and dried over anhydrous magnesium sulphate. Filtration and removal of the solvent *in vacuo* yielded the title compound.

EXAMPLE 143

N^1-Acetyl-N^8-benzyloxycarbonyl-N^4-[N-(tert-butoxycarbonyl)-D-phenylalanyl-L-prolyl]-2,2-difluoro-3-hydroxy-1,4,8-octanetriamine

The title compound was prepared from the amine of Example 142 and N-(tert-butoxycarbonyl)-D-phenylalanyl-L-proline by the procedure described in Example 5.

EXAMPLE 144

N^1-Acetyl-N^4-[N-(tert-butoxycarbonyl)-D-phenylalanyl-L-prolyl]-2,2-difluoro-3-hydroxy-1,4,8-octanetriamine

The title compound was prepared from the carbamate of Example 143 by the procedure described in Example 6.

EXAMPLE 145

N^1-Acetyl-N^8-(tert-butoxycarbonyl)-N^4-[N-(tert-butoxycarbonyl)-D-phenylalanyl-L-prolyl]-2,2-difluoro-3-hydroxy-1,4,8-octanetriamine

The title compound was prepared from the amine of Example 144 and di-tert-butyldicarbonate by the procedure described in Example 127.

EXAMPLE 146

N^1-Acetyl-N^8-(tert-butoxycarbonyl)-N^4-[N-(tert-butoxycarbonyl)-D-phenylalanyl-L-prolyl]-2,2-difluoro-3-oxo-1,4,8-octanetriamine

The title compound was prepared from the alcohol of Example 145 by the procedure described in Example 8.

EXAMPLE 147

N^1-Acetyl-N^4-(D-phenylalanyl-L-prolyl)-2,2-difluoro-3-oxo-1,4,8-octanetriamine, bishydrochloride

The title compound was prepared from the ketone of Example 146 by the procedure described in Example 64.

The foregoing describes in detail the generic and specific aspects of the scope of the invention as well as the manner of making and using the invention.

By following the techniques referenced above, as well as by utilization of other known techniques, as well as by comparison with compounds known to be useful for treatment of the above-mentioned disease states, it is believed that adequate material is available to enable one of ordinary skill in the art to practice the invention. Of course, in the end-use application of the compounds of this invention, the compounds are preferably formulated into suitable pharmaceutical preparations such as tablets, capsules or elixers, for oral administration or in sterile solutions or suspensions for parenteral administration. The compounds of this invention can be administered to patients (animals and human) in need of such treatment in a dosage range of 5 to 500 mg per patient generally given several times, thus giving a total daily dose of from 5 to 2000 mg per day. As stated above, the dose will vary depending on severity of disease, weight of patient and other factors which a person skilled in the art will recognize.

Typically the compounds described above are formulated into pharmaceutical compositions as discussed below.

About 10 to 500 mg of a compound or mixture of compounds of formula I or a physiologically acceptable salt is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in these compositions or preparations is such that a suitable dosage in the range indicated is obtained.

Illustrative of the adjuvants which may be incorporated in tablets, capsules and the like are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as microcrystalline cellulose; a disintegrating agent such as corn starch, pregelatinized starch, alginic acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as peppermint, oil of wintergreen or cherry. When the dosage unit form is a capsule, it

may contain in addition to materials of the above type, a liquid carrier such as fatty oil. Various other materials may he present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixer may contain the active compound, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Sterile compositions for injection can be formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection, a naturally occurring vegetable oil like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or a synthetic fatty vehicle like ethyl oleate or the like. Buffers, preservatives, antioxidants and the like can be incorporated as required.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

Claims

1. A compound of the formulae

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_bC(O)XR_a)_nQ$ **A**

and

$R_1NHCHR_2C(O)CF_2CHR_3NHC(O)X'$ **B**

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R'_1 is an α-amino acid protecting group of Group K', an α-amino acid or a peptide comprised of 2 to 8 α-amino acid units, the terminal amine of said α-amino acid and peptide bearing a protecting group of Group K',

R_1 is H, an α-amino protecting group of Groups K' and K, an α-amino acid or a peptide comprised of 2 to 8 α-amino acid units, the terminal amine of said α-amino acid and peptide optionally bearing a protecting group of Groups K' and K,

R_2 is a side chain of an α-amino acid, CHM or a moiety of Group J,

R_3 is H, C_{1-7} alkyl, phenyl, phenethyl, benzyl, cyclohexyl, cyclohexylmethyl, 2-pyridylalkyl, or is an α-amino acid side chain,

n is an integer of 1 to 10,

R_a is a side chain of an α-amino acid, CHM or is an ethylene moiety which when attached to the nitrogen atom of a retroamide forms a 2-oxopyrrolidine moiety,

R_b is H, C_{1-7} alkyl or an ethylene moiety which when linked to the CH moiety of X forms a 2-oxopyrrolidine moiety,

X is H, CH, OR_7 or R_7, with R_7 being a C_{1-7} alkyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl or 2-pyridylalkyl, with the proviso that when X is other than CH, R_a and Q are deleted,

X' is H, C_{1-7} alkyl, phenyl, phenethyl, benzyl, cyclohexyl, cyclohexylmethyl, 2-pyridylalkyl or an amino β halo C_{1-6} alkylene,

Q is H, C_{1-10} alkyl, C_{7-10} aralkyl, $C(O)R_5Y$ or C(O)Y,

R_5 is an α-amino acid or a peptide comprised of 2 to 5 α-amino acid units,

Y is NHR_4 or OR_4, and

R_4 is H, C_{1-7} alkyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl or 2-pyridylalkyl, and

the α-amino acid or peptide moieties being selected from Groups A, B, C, C', D, E, E', F, F', G, G', J, K and K', said groups being

A: Lys and Arg

B: Glu, Asp

C: Ser, Thr, Gln, Asn, Cys, His, (3-pyrazolyl)Ala, (4-pyrimidinyl)Ala, and N-methyl derivatives

C': Ser, Thr, Gln, Asn and Cys, and their N-methyl derivatives.

D: Pro, Ind

E: Ala, β-Ala, Leu, Ile, Val, n-Val, β-Val, Met, CHM, β-Valine, β-Alanine, n-Leu and N-methyl derivatives (β-representing beta),

E': Leu, Ile, n-Val, Met, n-Leu, CHM and their N-methyl derivatives,

F: Phe, Tyr, CHM, O-Methyl Tyrosine, (3-pyrazolyl)Ala, (4-pyrimidinyl)Ala, Trp, Nal(1), and N-methyl

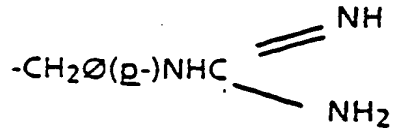
derivatives

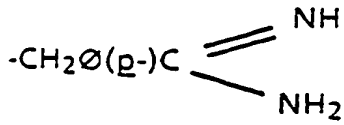
F′: Phe, Tyr, O-methyl tyrosine, Trp, Nal-(l) and their N-methyl derivatives,

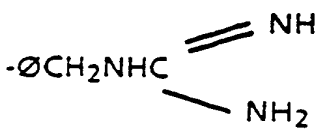
G: Gly, Sar

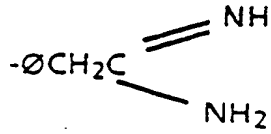
G′: Gly,

J:


(J-1)


(J-2)

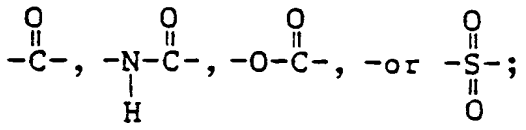

(J-3) and


(J-4)

with ø, of course, representing phenyl (it being understood that the bond of J1-4 is always attached to an amino acid),

K: Acetyl (Ac), Succinyl (suc), Benzoyl (Bz), t-Butyloxycarbonyl (Boc), Carbobenzoxy (CBZ), Tosyl (Ts), Dansyl (DNS), Isovaleryl (Iva), Methoxysuccinyl (MeOSuc), 1-Adamantanesulphonyl ($AdSO_2$), 1-Adamantaneacetyl (AdAc), 2-Carboxybenzoyl (2-CBZ), Phenylacetyl, t-Butylacetyl (Tba), bis [(1-naphthyl)-methyl]acetyl (BNMA),

K′: is -A-Rz wherein A is



and Rz is an aryl group containing 6, 10 or 12 carbons suitably substituted by 1 to 3 members selected independently from the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido containing from 1 to 15 carbons, provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro.

2. Compounds of Claim 1 which are compounds of the formula

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ Ia

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R'_1 is $P_2P_3P_4$ having a Group K′ protecting group on its terminal amine,

P_2 is an amino acid of Groups D, E and F, preferably Pro,

P_3 is an amino acid of Groups D and E and Lys,

P_4 is an amino acid of Group E or is zero,

R_2 is a side chain of an amino acid of Groups E and G,

R_3 is a side chain of an amino acid of Groups E and G,

R_a is a side chain of an amino acid of Groups E and G and Lys,

R_b, X, n and Q are as defined in Claim 1.

3. A compound of Claim 2, said compound being

4-Clø-SAC-Bz-Ala-Ala-Pro-Val-[CF_2GlyNH]m-Gly-NH_2,

4-Clø-SAC-Bz-Ala-Ile-Pro-Val-[CF_2GlyNH]m-Ala-NH_2,

4-Clø-SAC-Bz[ϵN-2(CBZ)]-Lys-Pro-Val-[CF_2GlyNH]m-Ala-NH_2,

4-Clø-SAC-BZ-[ϵN-2(CBZ)]-Lys-Pro-Val-[CF_2GlyNH]m-Ala-OH,

4-Clø-SAC-Bz-[ϵN-2(CBZ)]-Lys-Pro-Val-[CF_2GlyNH]m-Ala-OMe,

4-Clø-SAC-Bz-Ala-Ala-Pro-Val-[CF_2GlyNH]C(O)CH_3,

ø-SAC-Bz-Val-Pro-Val[CF_2GlyNH]C(O)CH_2ø,

4-Clø-SAC-Bz-Val-Pro-Val-[CF_2GlyNH]C(O)CH_2ø,
4-Brø-SAC-Bz-Val-Pro-Val-[CF_2GlyNH]C(O)CH_2ø,
ø-SAC-Bz-Val-Pro-Val-[CF_2GlyNH]C(O)CH_2ø, or
4-Clø-SAC-Bz-Val-Pro-Val-[CF_2GlyNH]C(O)CH_3.

4. Compounds of Claim 1 which are compounds of the formula
R'_1-NHCHR_2C(O)CF_2CHR_3(NR_b-C(O)XR_a)$_n$Q Ib
and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
R'_1 is $P_2P_3P_4$ having a Group K′ protecting group on its terminal amine,
P_2 is an amino acid of Groups D, E and G,
P_3 is an amino acid of Groups E and G, or is deleted,
P_4 is an amino acid of Groups E and G, or is deleted,
with Ala being preferred,
R_2 is a side chain of an amino acid of Groups E and F,
R_3 is as defined in formula A with the amino acid side chain selected from amino acids of Groups E and G,
R_a, R_b, X, n and Q are as defined in Claim 1.

5. A compound of Claim 4, said compound being
4-Clø-SAC-Bz-Ala-Ala-Pro-Phe-[CF_2-Gly-NH]C(O)CH_3,
4-Clø-SAC-Bz-Ala-Ala-Pro-Phe-[CF_2-Phe-NH]C(O)CH_3,
4-Clø-SAC-Bz-Ala-Ala-Pro-Phe-[CF_2-Ala-NH]C(O)$_2CH_3$, or
4-Clø-SAC-Bz-Ala-Ala-Pro-Phe-[CF_2-Ala-NH]C(O)$_2$Et.

6. Compounds of Claim 1 which are compounds of the formula
R'_1-NHCHR_2C(O)CF_2CHR_3(NR_b-C(O)XR_a)$_n$Q Ic
and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
R'_1 is a protecting group of Group K′, (a) P_2P_3 or (b) $P_2P_3P_4$ the terminal amine of (a) and (b) having a protecting group of Group K′.
(a) P_2 is an amino acid of Groups D, E and F,
P_3 is an amino acid of Group F,
(b) P_2 is an amino acid of Group E,
P_3 is an amino acid of Groups C, E and G,
P_4 is an amino acid of Groups E, F and G or is zero,
R_2 is a side chain of an amino acid of Group A, or a moiety of Group J,
R_3 is as defined in Claim 1 with the side chain of an amino acid being of Groups C and G,
R_5 is an amino acid of Groups C′, E and D or is zero,
R_a is a side chain of an amino acid of Groups C and G, and
R_b, X, n and Q are as defined in Claim 1.

7. A compound of Claim 6, said compound being
4-Clø-SAC-Bz-(D)-Phe-Pro-JI-[CF_2-Gly-NH]C(O)C_3H_7,
4-Clø-SAC-Bz-(D)-Phe-Pro-Arg-[CF_2-Gly-NH]C(O)C_3H_7,
4-Clø-SAC-Bz-Arg-[CF_2-Gly-NH]C(O)C_3H_7,
4-Clø-SAC-Bz-Phe-Ser-Ala-[CF_2-Gly-NH]C(O)C_3H_7,
4-Clø-SAC-Bz-(D)-Phe-Pro-Lys-[CF_2-Gly-NH]C(O)CH_3, or
4-Clø-SAC-Bz-JI-[CF_2-Gly-NH]C(O)CH_3.

8. Compounds of Claim 1 which are compounds of the formula
R'_1-NHCHR_2C(O)CF_2CHR_3(NR_b-C(O)XR_a)$_n$Q Id
and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
R'_1 is a protecting group of Group K′ or $P_2P_3P_4$, the terminal amine of which bears a Group K′ protecting group,
P_2 is an amino acid of Groups D, E and G or is deleted,
P_3 is an amino acid of Groups E and G or is deleted,
P_4 is an amino acid of Groups E and G or is deleted,
R_2 is a side chain of an amino acid of Groups E and F, and
R_3, R_a, R_b, X, n and Q are as defined in Claim 1.

9. A compound of Claim 8, said compound being
4-Clø-SAC-Bz-Phe-[CF_2-Gly-NH]C(O)CH_3,
4-Clø-SAC-Bz-Phe-[CF_2-Gly-NH]C(O)OMe,
4-Clø-SAC-Bz-Tyr-[CF_2-Gly-NH]C(O)CH_3,
4-Clø-SAC-Bz-Tyr-[CF_2-Gly-NH]C(O)OMe, or
CBZ-Leu-Phe-[CF_2Gly-NH]C(O)CH_3.

10. Compounds of Claim I which are compounds of the formula

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ Ie

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R'_1 is a protecting group of Group K', P_2P_3 or $P_2P_3P_4$, the terminal amines of which bear a protecting group of Group K',

(a) P_2P_3 is

P_2 is an amino acid of Groups E and F,

P_3 is an amino acid of Group F,

(b) $P_2P_3P_4$ is

P_2 is an amino acid of Groups D and E,

P_3 is an amino acid of Groups E and G,

P_4 is an amino acid of Groups E and G or is zero, and

R_2, R_3, R_a, R_b, n, X and Q are as defined in Claim 6.

11. A compound of Claim 10, said compound being

4-Clø-SAC-Bz-(D)-Phe-Pro-Jl-[CF_2-Gly-NH]C(O)C_3H_7,

4-Clø-SAC-Bz-(D)-Phe-Pro-Arg-[CF_2-Gly-NH]C(O)C_3H_7,

4-Clø-SAC-Bz-Arg-[CF_2-Gly-NH]C(O)C_3H_7,

4-Clø-SAC-Bz-Phe-Ser-Ala-[CF_2-Gly-NH]C(O)C_3H_7,

4-Clø-SAC-Bz-(D)-Phe-Pro-Lys-[CF_2-Gly-NH]C(O)CH_3, or

4-Clø-SAC-Bz-Jl-[CF_2-Gly-NH]C(O)CH_3.

12. Compounds of Claim 1 which are compounds of the formula

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ If

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R'_1 is P_2P_3, the terminal amine of which bears a protecting group of Group K',

P_2 is an amino acid of Groups E and F,

P_3 is an amino acid of Groups B and F,

R_2 is a side chain of an amino acid of Group A or a moiety of Group J,

R_3, R_a, R_b, X, n and Q are as defined in Claim 1.

13. A compound of Claim 12, said compound being

4-Clø-SAC-Bz-Glu-Phe-Lys[CF_2-Gly-NH]m-Ala-OH,

4-Clø-SAC-Bz-Glu-Phe-Lys[CF_2-Gly-NH]$\overline{m}$-Ala-NH_2,

4-Clø-SAC-Bz-Glu-Phe-Lys[CF_2-Gly-NH]$\overline{m}$-Ala-OCH_3,

4-Clø-SAC-Bz-Ala-J-l[CF_2-Gly-NH]$\overline{COCH_3}$, or

4-Clø-SAC-Bz-Ala-Lys-[CF_2-Gly-NH]$COCH_3$.

14. Compounds of Claim I which are compounds of the formula

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ Ig

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof wherein

R'_1 is P_2, the terminal amine of which bears a protecting group of Group K',

P_2 is an amino acid of Groups, A, B, C, D, E, F and G,

R_2 is a side chain of an amino acid of Group A or a moiety of Group J,

R_a is the side chain of an amino acid of Groups E and G,

R_3, R_b, X, n and Q are as defined in Claim 1.

15. A compound of Claim 14, said compound being

4-Clø-SAC-Bz-Ala-Arg-[CF_2-Gly-NH]$COCH_3$,

4-Clø-SAC-Bz-Ala-Arg-[CF_2-Gly-NH]$COCCH_3$,

4-Clø-SAC-Bz-Ala-Arg-[CF_2-Gly-NH]m-Gly-NH_2, or

4-Clø-SAC-Bz-Ala-J-l[CF_2-Gly-NH]$C\overline{O}CH_3$.

16. Compounds of Claim I which are compounds of the formula

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ Ih

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R'_1 is P_2P_3, the terminal amine of which bears a protecting group of Group K',

P_2 is an amino acid of Groups E and F,

P_3 is an amino acid of Groups E and F,

R_2 is a side chain of an amino acid of Group A or a moiety of Group J,

R_3 is a side chain of an amino acid of Groups E or G,

R_a is a side chain of an amino acid of Group E or Gly,

R_b, X, n and Q are as defined in Claim 1.

17. A compound of Claim 16, said compound being

4-Clø-SAC-Bz-Leu-Ala-Arg-[CF_2-Gly-NH]$COCH_3$,
4-Clø-SAC-Bz-Leu-Ala-Arg-[CF_2-Gly-NH]$COCCH_3$,
4-Clø-SAC-Bz-Leu-Ala-Arg-[CF_2-Gly-NH]COC-Benzyl, or
4-Clø-SAC-Bz-Leu-Ala-Arg-[CF_2-Gly-NH]m-Ala-NH_2.

18. Compounds of Claim I which are compounds of the formula

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ Ii

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
R'_1 is P_2P_3, the terminal amine of which bears a protecting group of Group K',
P_2 is an amino acid of Groups E and G,
P_3 is an amino acid of Group B,
R_2 is a side chain of an amino acid of Group A or a moiety of Group J,
R_3 is a side chain of an amino acid of Group E,
R_a is a side chain of an amino acid of Group E,
R_b, X, n and Q are as defined in Claim 1.

19. A compound of Claim 18, said compound being
K'-Glu-Gly-Arg-[CF_2-Ala-NH]m-Ala-NH_2,
K'-Glu-Gly-Arg-[CF_2-Ala-NH](Ala)CHO,
K'-Glu-Gly-Arg-[CF_2-Ala-NH](Ala)$C(O)_2CH_3$,
K'-Glu-Gly-(p-gua)-Phe-[CF_2-Ala-NH](Ala)H, said K' being
4-Clø-SAC-Bz, 4-Brø-SAC-Bz or ø-SAC-Bz.

20. Compounds of Claim I which are compounds of the formula

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ Ij

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
R'_1 is P_2P_3, the terminal amine of which bears a protecting group from Group K',
P_2 is Gly,
P_3 is an amino acid of Group B,
R_2 is a side chain of an amino acid of Group A or a moiety of Group J,
R_3 is a side chain of an amino acid of Groups E and F,
R_a is a side chain of an amino acid of Group E, and
R_b, X, n and Q are as defined in Claim 1.

21. A compound of Claim 20, said compound being
4-Clø-SAC-Bz-Glu-Gly-Arg-[CF_2-Ala-NH](Ala)CHO,
4-Clø-SAC-Bz-Glu-Gly-(p-gua)-Phe-[CF_2-Ala-NH](Ala)H, or
4-Clø-SAC-Bz-Glu-Gly-Arg-[CF_2-Ala-NH]m-Ala-NH_2.

22. Compounds of Claim I which are compounds of the formula

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ Ik

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
R'_1 is a protecting group of Group K' or P_2P_3, the terminal amine of which bears a protecting group of Group K',
P_2 is an amino acid of Group E or is deleted,
P_3 is an amino acid of Group E, or is deleted,
R_2 is a side chain of an amino acid of Group A or a moiety of Group J,
R_3 is a side chain of an amino acid of Groups E and G,
R_a is a side chain of an amino acid of Group E,
R_b, X, n and Q are as defined in Claim 1.

23. A compound of Claim 22, said compound being
4-Clø-SAC-Bz-Leu-Leu-Arg-[CF_2-Gly-NH](Ala)CHO,
4-Clø-SAC-Bz-Leu-Leu-p-gua-Phe-[CF_2-Gly-NH]m-Ala-NH_2,
4-Clø-SAC-Bz-Leu-Leu-Arg-[CF_2-Gly-NH]m-Ala-OH,
4-Clø-SAC-Bz-Leu-Leu-Arg-[CF_2-Gly-NH]$COCH_3$, or
4-Clø-SAC-Bz-J-I-[CF_2-Gly-NH]$COCH_3$.

24. Compounds of Claim I which are compounds of the formula

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ Il

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, with the proviso that the P_1 carbonyl moiety may exist in its chemically reduced form, wherein
R'_1 is a protecting group of Group K',
R_2 is a side chain of an amino acid of Groups C, E and G,
R_3 is a side chain of an amino acid of Groups E and G,

R_a, R_b, X, n and Q are as defined in Claim 1.

25. A compound of Claim 24, said compound being
4-Clø-SAC-Bz-NHCH$_2$C(O)[CF$_2$-Gly-NH]COCH$_3$, or
4-Clø-SAC-Bz-NHCH$_2$CHOH[CF$_2$-Gly-NH]COCH$_3$.

26. Compounds of Claim I which are compounds of the formula
R$'$·NHCHR$_2$C(O)CF$_2$CHR$_3$(NR$_b$-C(O)XR$_a$)$_n$Q Im
and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
R$'$ is P$_2$, the terminal amine of which bears a protecting group of Group K$'$,
P$_2$ is Nε-Ac-Lys or is an amino acid of Groups C and E,
R$_2$ is the side chain of D-Ala,
R$_3$ is a side chain of an amino acid of Group E,
R_a, R_b, X, n and Q are as defined in Claim 1.

27. A compound of Claim 26, said compound being
4-Clø-SAC-Bz-(Nε-Ac-Lys)-D-Ala[CF$_2$-Ala-NH]CHO, or
4-Clø-SAC-Bz-(Nε-Ac-Lys)-D-Ala[CF$_2$-Ala-NH]m-Gly-OH.

28. Compounds of Claim I which are compounds of the formula
R$'$·NHCHR$_2$C(O)CF$_2$CHR$_3$(NR$_b$-C(O)XR$_a$)$_n$Q In
and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
R$'$ is P$_2$P$_3$, the terminal amine of which is a protecting group of Group K$'$,
P$_2$ is an amino acid of Groups E and F,
P$_3$ is an amino acid of Groups E and F or is deleted,
R$_2$ is a side chain of an amino acid of Group A, Thr-O-Benzyl or a moiety of Group J,
R$_3$ is a side chain of an amino acid of Groups E and G,
R_a, R_b, X, n and Q are as defined in Claim 1.

29. A compound of Claim 28, said compound being
4-Clø-SAC-Bz-Phe-J-I[CF$_2$-Gly-NH]COCH$_3$,
4-Clø-SAC-Bz-Leu-Leu-J-I[CF$_2$-Gly-NH]m-Gly-OH, or
4-Clø-SAC-Bz-Leu-Leu-Arg[CF$_2$-Gly-NH]m-Gly-OH.

30. Compounds of Claim 1 which are compounds of the formula
R$'$·NHCHR$_2$C(O)CF$_2$CHR$_3$(NR$_b$-C(O)XR$_a$)$_n$Q Io
and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, with the proviso that the carbonyl moiety of P$_1$ may exist in its chemically reduced form, wherein
R$'$ is P$_2$P$_3$P$_4$P$_5$, the terminal amine of which bears a protecting group of Group K$'$,
P$_2$ is an amino acid, or its N-methyl derivatives of Groups C, E and F, (3-pyrazolyl)Ala or (4-pyrimidin-yl)-Ala,
P$_3$ is an amino acid of Groups E and F, or is deleted,
P$_4$ is an amino acid of Groups D, E and F, or is deleted,
P$_5$ is an amino acid of Groups C, E and F, or is deleted,
R$_2$ is a side chain of an amino acid of Groups E and F or CHM,
R$_3$ is a side chain of an amino acid of Groups E and G,
R_a is a side chain of Groups E and G,
R_b, X, n and Q are as defined in Claim 1.

31. A compound of Claim 30, said compound being
4-Clø-SAC-Bz-Nal(1)-His-Leu[CF$_2$-Gly-NH](Val)C(O)-Benzyl,
4-Clø-SAC-Bz-Nal(1)-His-Leu[CF$_2$-Gly-NH]m-Val-NH-Benzyl,
4-Clø-SAC-Bz-Phe-His-Leu-[CF$_2$-Gly-NH]m-Val-NH-Benzyl,
4-Clø-SAC-Bz-Phe-n-Val-Leu-[CF$_2$-Gly-NH]m-Val-NH-Benzyl,
4-Clø-SAC-Bz-Phe-n-Val-Leu-[CF$_2$-Gly-NH]m-Val-NH-Benzyl,
4-Clø-SAC-Bz-Phe-n-Val-Leu-[CF$_2$-Gly-NH]m-Ile-NH-2-pyridylmethyl,
4-Clø-SAC-Bz-His-Pro-Phe-His-Leu[CF$_2$-Val-NH]m-Ile-His-OH,
4-Clø-SAC-Bz-His-Pro-Phe-His-Leu[CF$_2$-Val-NH]m-Ile-His-NH$_2$,
4-Clø-SAC-Bz-Phe-His-CHM-[CF$_2$-Gly-NH](Val)C(O)-benzyl,
4-Clø-SAC-Bz-Phe-His-CHM-[CF$_2$-Gly-NH]m-Ile-NH-2-pyridylmethyl,
4-Clø-SAC-Bz-Phe-n-Val-Leu[CF$_2$-Gly-NH](Val)CO-benzyl,
4-Clø-SAC-Bz-His-Leu-[CF$_2$-Gly-NH]m-Val-NH-benzyl,
4-Clø-SAC-Bz-Phe-His-Leu[CF$_2$-Gly-NH]m-Val-NH-benzyl,
4-Clø-SAC-Bz-Phe-n-Val-Leu[CF$_2$-Gly-NH]m-Ala-NH-benzyl,
4-Clø-SAC-Bz-Phe-n-Val-Leu[CF$_2$-Gly-NH]m-Gly-NH-benzyl,

4-Clø-SAC-Bz-Phe-n-Val-Leu[CF_2-Gly-NH]Iva,
4-Clø-SAC-Bz-Phe-n-Val-Leu[CF_2-Gly-NH]CO_2(1-methylpropyl),
4-Clø-SAC-Bz-Phe-n-Val-CHM-[CF_2-Gly-NH]m-Val-NH-benzyl,
4-Clø-SAC-Bz-Phe-n-Val-CHM-[CF_2-Gly-NH]Iva,
4-Clø-SAC-Bz-Phe-n-Val-Leu-[CF_2-Gly-NH]CO[1-(1-methylpropyl)-4-phenylbutyl],
4-Clø-SAC-Bz-(O-Me)Tyr-n-Val-CHM-[CF_2-Val-NH]Iva,
4-Clø-SAC-Bz-Phe-(3-pyrazolyl)Ala-CHM-[CF_2-Val-NH]Iva,
4-Clø-SAC-Bz-(O-Me)Tyr-n-Val-CHM-[CF_2-Val-NH]Iva, or
4-Clø-SAC-Bz-(O-Me)Tyr-(4-pyrimidinyl)Ala-CHM-[CF_2-Val-NH]Iva.

32. Compounds of Claim I, which are compounds of the formula

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ Ip

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, with the proviso that the P1 carbonyl moiety may exist in its chemically reduced form, wherein

R'_1 is P_2P_3, the terminal amine of which bears a protecting group of Group K',
P_2 is an amino acid of Groups E and F,
P_3 is an amino acid of Groups E and F, or is deleted,
R_2 is a side chain of an amino acid of Groups E and F,
R_3 is a side chain of an amino acid,
R_a, R_b, X, n and Q are as defined in Claim 1.

33. A compound of Claim 32, said compound being
4-Clø-SAC-Bz-Val-Leu[CF_2-Gly-NH](Ala)Iva,
4-Clø-SAC-Bz-Val-Val-Leu[CF_2-Gly-NH](Ala)Iva,
4-Clø-SAC-Bz-Val-Leu[CF_2-Gly-NH]m-Ala-Iaa, or
4-Clø-SAC-Bz-Val-Val-Leu[CF_2-Gly-NH]m-Ala-Iaa.

34. Compounds of Claim I which are compounds of the formula

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ Iq

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R'_1 is P_2P_3, the terminal amine of which bears a protecting group of Group K',
P_2 is an amino acid of Groups E and F,
P_3 is an amino acid of Groups E and F or is deleted,
R_2 is a side chain of an amino acid of Groups E and F,
R_3 is Gly or Phe,
R_a, R_b, X, n and Q are as defined in Claim 1.

35. A compound of Claim 34, said compound being
4-Clø-SAC-Bz-Val-Val-Phe-[CF_2-Phe-NH](Ala)Iva,
4-Clø-SAC-Bz-Val-Val-Phe-[CF_2-Phe-NH]m-Ala-$NHCH_2CH(CH_3)_2$,
4-Clø-SAC-Bz-Val-Ala-Phe[CF_2-Gly-NH](Ala)Iva, or
4-Clø-SAC-Bz-Val-Phe[CF_2-Gly-NH]m-Ala-Phe-OCH_3.

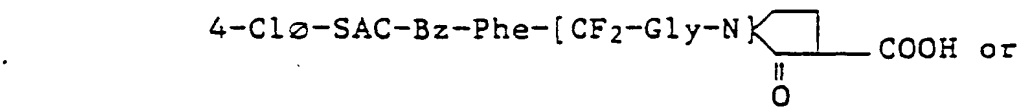
36. Compounds of Claim I which are compounds of the formula

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ Ir

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R'_1 is a protecting group of Group K',
R_2 is a side chain of an amino acid of Groups E, F and G,
R_3 is a side chain of an amino acid of Groups E or Gly,
R_a, R_b, X, n and Q are as defined in Claim 1.

37. A compound of Claim 36, said compound being
4-Clø-SAC-Bz-Phe-[CF_2-Gly-NCH_3]m-Gly-OH,
4-Clø-SAC-Bz-Phe-[CF_2-Gly-NH]m-Gly-OH,



4-Clø-SAC-Bz-Phe-[CF_2-Ala-NH]m-Gly-OH.

38. Compounds of Claim I which are compounds of the formula

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_n$ Is

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R'_1 is P_2P_3, the terminal amine of which is a protecting group of Group K',
P_3 is an amino acid of Group F or is deleted,
R_2 is the side chain of Gly,
R_3 is the side chain of an amino acid of Group F,
R_a, R_b, X, n and Q are as defined in Claim 1.

39. A compound of Claim 38, said compound being
4-Clø-SAC-Bz-Tyr-Gly-Gly-[CF_2-Phe-NH]m-Met-OH, or
4-Clø-SAC-Bz-Tyr-Gly-Gly-[CF_2-Phe-NH]m-Leu-OH.

40. Compounds of Claim I which are compounds of the formula

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ It

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
R'_1 is P_2, the terminal amine of which bears a protecting group of Group K',
P_2 is an amino acid of Group E,
R_2 is a side chain of an amino acid of Groups E and G,
R_3 is a side chain of an amino acid of Group E,
R_a, R_b, X, n and Q are as defined in Claim 1.

41. A compound of Claim 40, said compound being
4-Clø-SAC-Bz-Ala-Ala-[CF_2-Ile-NH]m-Ala-NH_2.

42. Compounds of Claim I which are compounds of the formula

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ Iu

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
R'_1 is a protecting group of Group K',
R_2 is a side chain of an amino acid of Groups A, B, E and F, a moiety of Group J or CHM,
R_3 is a side chain of amino acids of Group E and Gly or CHM,
R_a, R_b, X, n and Q are as defined in Claim 1.

43. A compound of Claim 42, said compound being
K'-Leu[CF_2-CHM-NH](Ala)Iva,
K'-Phe[CF_2-CHM-NH]m-Gly-OH,
H-CHM[CF_2-Ala-NH](Gly)Iva,
K'-Leu[CF_2-CHM-NH]m-Ala-NH-benzyl,
K'-Leu[CF_2-Gly-NH]m-CHM-NH-benzyl, or
K'-Leu[CF_2-Gly-NH](CHM)CO-benzyl, K' being 4-Clø-SAC-Bz,
4-Brø-SAC-Bz or ø-SAC-Bz.

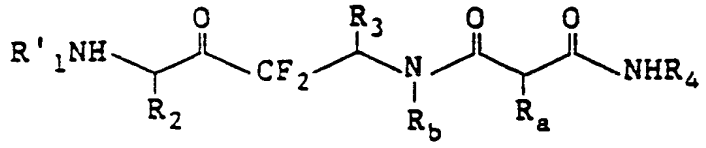
44. Compounds of Claim I which are compounds of the formula

$R'_1NHCHR_2C(O)CF_2CHR_3(NR_b\text{-}C(O)XR_a)_nQ$ Iv

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
R'_1 is P_2P_3, the terminal amine of which bears a protecting group of Group K',
P_2 is an amino acid of Groups E and F,
P_3 is an amino acid of Groups C, E and F,
R_2 is a side chain of an amino acid of Group A or a moiety of Group J,
R_3 is the side chain of Gly,
R_a, R_b, X, n and Q are as defined in Claim 1.

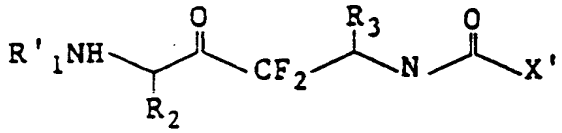
45. A compound of Claim 44, said compound being
4-Clø-SAC-Bz-(D)-Pro-Phe-Arg-[CF_2-Gly-NH]$COCH_3$,
4-Clø-SAC-Bz-(D)-Pro-Phe-Arg-[CF_2-Gly-NH]COOMe,
4-Clø-SAC-Bz-(D)-Pro-Phe-Arg-[CF_2-Gly-NH]m-Gly-NH_2, or
4-Clø-SAC-Bz-(D)-Pro-Phe-J-1-[CF_2-Gly-NH]$COCH_3$.

46. Compounds of Claim 1 which are compounds of the formula



Iwa

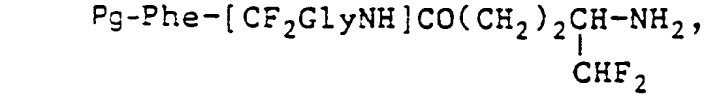
and



Iwb

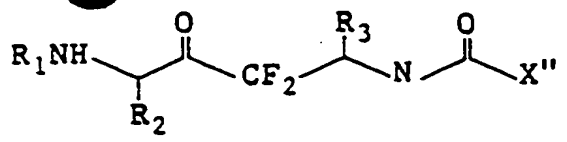
and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
R'_1 is H, an amino protecting group of Group K', or $P_2P_3P_4$, the terminal amines of which bear a protecting group of Group K',
P_2 is an amino acid of Groups C', E', F' and G' or is deleted,
P_3 is an amino acid of Groups C', E', F' and G' or is deleted,
P_4 is an amino acid of Group C', β-Ala, β-Val or is deleted,
R_2 is the side chain of an amino acid of Groups E' and F' or CHM,
R_3 is the side chain of an amino acid of Groups E' and G',
R_a is the side chain of an amino acid of Group E' or Val,
R_b is H or C_{1-6} alkyl,
R_4 is H, C_{1-6} alkyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl or 2-pyridylmethyl,
X' is amino-β-halo C_{1-6} alkylene or R_4.

47. A compound of Claim 46, said compound being
Pg-Ser-Gln-Asn-Tyr[CF_2GlyNH]m-LeuNH_2,
Pg-Thr-Gln-Asn-Tyr[CF_2GlyNH]$\overline{m}$-LeuNHCHM,
Pg-Ser-Gln-Asn-Tyr[CF_2GlyNH]$\overline{C}$(O)H,
Pg-Ser-Gln-Asn-Tyr[CF_2GlyNH]C(O)CHM,
Pg-β-Ala-(O-Me)-Tyr-n-Val-CHM-[CF_2GlyNH]Iva,
Pg-Phe-n-Val-CHM-[CF_2GlyNH]Iva,
Pg-Ser-Gln-Asn-Tyr-[CF_2IleNH]Iva,
Pg-Ser-Phe-n-Val-CHM-[CF_2GlyNH]Iva,
Pg-Ser-Gln-Asn-Phe-[CF_2GlyNH]mValNH_2,
Pg-Ser-Gln-Asn-Tyr-[CF_2IleNH]$\overline{m}$ValNH_2,
Pg-Phe-[CF_2GlyNH]$COCH_2C_6H_5$,
Pg-Leu-[CF_2GlyNH](Val)$COCH_2C_6H_5$,
Pg-Phe-nVal-Leu-[CF_2GlyNH]mValN$HCH_2C_6H_5$,
Pg-Tba-Phe-nVal-Leu-[CF_2Gly$\overline{N}$H]$\overline{m}$ValN$HCH_2C_6H_5$,
Pg-Phe-nVal-CHM-[CF_2GlyNH]Iva,
Pg-(OMe)-Tyr-nVal-CHM-[CF_2GlyNH]Iva,
Pg-Phe-nVal-Leu-[CF_2GlyNH]Iva,
Pg-Phe-[CF_2GlyNH]$CO(CH_2)_3NH_2$,
Pg-Phe-[CF_2GlyNH]$COCH_2CF_2CH_2NH_2$, or



wherein Pg is 4-Clø-SAC-Bz,
4-Brø-SAC-Bz, or ø-SAC-Bz.

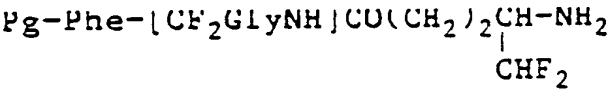
48. Compounds of Claim 1 which are compounds of the formula



Iwb'

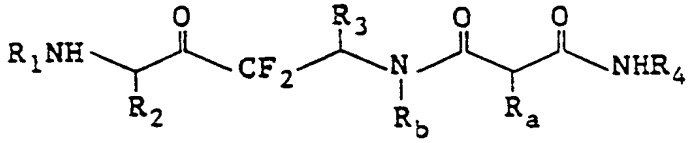
and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
R_1 is H, an amino protecting group of Groups K and K', or $P_2P_3P_4$, the terminal amines of which bear a protecting group of Group K',
P_2 is an amino acid of Groups C', E', F' and G' or is deleted,
P_3 is an amino acid of Groups C', E', F' and G' or is deleted,
P_4 is an amino acid of Group C', β-Ala, β-Val or is deleted,
R_2 is the side chain of an amino acid of Groups E' and F' or CHM,
R_3 is the side chain of an amino acid of Groups E' and G',
R_a is the side chain of an amino acid of Group E' or Val,
X'' is amino-β-halo C_{1-6} alkylene.

49. A compound of Claim 48, said compound being
Pg-Phe-[CF_2GlyNH]CO$(CH_2)_3NH_2$,
Pg-Phe-[CF_2GlyNH]CO$CH_2CF_2CH_2NH_2$, or



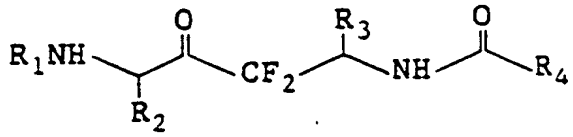
wherein Pg is 4-Clø-SAC-Bz, 4-Brø-SAC-Bz, ø-SAC-Bz, Iva, Boc, CBZ or Tba.

50. A use of a compound of formula Iwa-1 and Iwb-1 for the preparation of a pharmaceutical preparation for treating acquired immuno deficiency syndrome, said formulae being



Iwa-1

and



Iwb-1

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
R_1 is an amino acid protecting group of Group K, or $P_2P_3P_4$ the terminal amines of which optionally bear a protecting group of Group K,
P_2 is an amino acid of Groups C', E', F' and G' or is deleted,
P_3 is an amino acid of Groups C', E', F' and G' or is deleted,
P_4 is an amino acid of Group C', β-Ala, β-Val or is deleted,
R_2 is the side chain of an amino acid of Groups E' and F' or CHM,
R_3 is the side chain of an amino acid of Groups E' and G',
R_a is the side chain of an amino acid og Group E' or Val,
R_b is H or C_{1-6} alkyl,
R_4 is H, C_{1-6} alkyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl or 2-pyridylalkyl, and
the α-amino acid or peptide moieties being selected from Groups A, B, C, C', D, E, E', F, F', G, G', J and K, said groups being

A: Lys and Arg

B: Glu, Asp

C: Ser, Thr, Gln, Asn, Cys, His, (3-pyrazolyl)Ala, (4-pyrimidinyl)Ala, and N-methyl derivatives

C′: Ser, Thr, Gln, Asn and Cys, and their N-methyl derivatives,

D: Pro, Ind

E: Ala, β-Ala, Leu, Ile, Val, n-Val, β-Val, Met, CHM, β-Valine, β-Alanine, n-Leu and N-methyl derivatives (β- representing beta)

E′: Leu, Ile, n-Val, Met, n-Leu, CHM and their N-methyl derivatives,

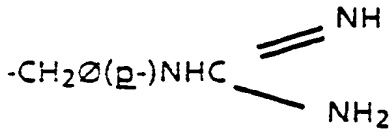
F: Phe, Tyr, CHM, O-Methyl Tyrosine, (3-pyrazolyl)Ala, (4-pyrimidinyl)Ala, Trp, Nal(1), and N-methyl derivatives

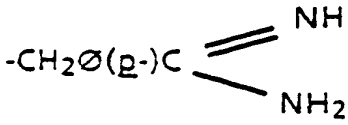
F′: Phe, Tyr, O-methyl tyrosine, Trp, Nal-(l) and their N-methyl derivatives,

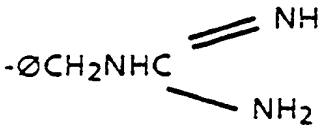
G: Gly, Sar

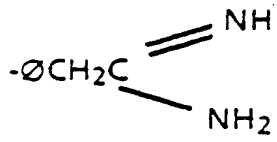
G′: Gly,

J:


(J-1)


(J-2)


(J-3) and


(J-4)

K: Acetyl (Ac), Succinyl (suc), Benzoyl (Bz), t-Butyloxycarbonyl (Boc), Carbobenzoxy (CBZ), Tosyl (Ts), Dansyl (DNS), Isovaleryl (Iva), Methoxysuccinyl (MeOSuc), 1-Adamantanesulphonyl ($AdSO_2$), 1-Adamantaneacetyl (AdAc), 2-Carboxybenzoyl (2-CBZ), Phenylacetyl, t-Butylacetyl (Tba), bis[(1-naphthyl)-methyl]acetyl (BNMA).

51. A use of a compound selected from Group Q for the preparation of a pharmaceutical preparation for treating acquired immuno deficiency syndrome, said Group Q being comprised of

Q-Ser-Gln-Asn-Tyr[CF_2GlyNH]m-$LeuNH_2$,

Q-Thr-Gln-Asn-Tyr[CF_2GlyNH]m-LeuNHCHM,

Q-Ser-Gln-Asn-Tyr[CF_2GlyNH]C(O)H,

Q-Ser-Gln-Asn-Tyr[CF_2GlyNH]C(O)CHM,

Q-β-Ala-(O-Me)-Tyr-n-Val-CHM-[CF_2GlyNH]Iva,

Q-Phe-n-Val-CHM-[CF_2GlyNH]Iva,

Q-Ser-Gln-Asn-Tyr-[CF_2IleNH]Iva,

Q-Ser-Phe-n-Val-CHM-[CF_2GlyNH]Iva,

Q-Ser-Gln-Asn-Phe-[CF_2GlyNH]m$ValNH_2$,

Q-Ser-Gln-Asn-Tyr-[CF_2IleNH]m$ValNH_2$,

Q-Phe-[CF_2GlyNH]$COCH_2C_6H_5$,

Q-Leu-[CF_2GlyNH](Val)$COCH_2C_6H_5$,

Q-Phe-nVal-Leu-[CF_2GlyNH]m$ValNHCH_2C_6H_5$,

Q-Phe-nVal-Leu-[CF_2GlyNH]m$ValNHCH_2C_6H_5$,

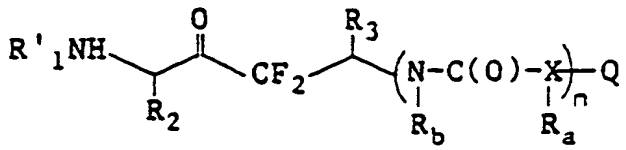
Q-Phe-nVal-CHM-[CF_2GlyNH]Iva,

Q-(OMe)-Tyr-nVal-CHM-[CF_2GlyNH]Iva,

Q-Phe-nVal-Leu-[CF_2GlyNH]Iva,

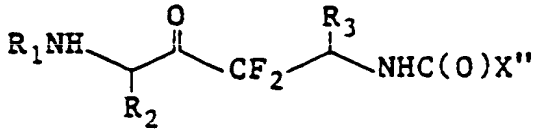
said Q being H, or an Iva, Boc, CBZ or Tba protecting group.

52. A process for preparing compounds of formulae



A

and



B

and the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

R'_1 is an α-amino acid protecting group of Group K', an α-amino acid or a peptide comprised of 2 to 8 α-amino acid units, the terminal amine of said α-amino acid and peptide bearing a protecting group of Group K',

R_1 is H, an α-amino protecting group of Groups K' and K, an α-amino acid or a peptide comprised of 2 to 8 α-amino acid units, the terminal amine of said α-amino acid and peptide optionally bearing a protecting group of Groups K' and K,

R_2 is a side chain of an α-amino acid, CHM or a moiety of Group J,

R_3 is H, C_{1-7} alkyl, phenyl, phenethyl, benzyl, cyclohexyl, cyclohexylmethyl, 2-pyridylalkyl, or is an α-amino acid side chain,

n is an integer of 1 to 10,

R_a is a side chain of an α-amino acid, CHM or is an ethylene moiety which when attached to the nitrogen atom of a retroamide forms a 2-oxopyrrolidine moiety,

R_b is H, C_{1-7} or an ethylene moiety which when linked to the CH moiety of X forms a 2-oxopyrrolidine moiety,

X is H, CH, CR_7 or R_7, with R_7 being a C_{1-7} alkyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl or 2-pyridylalkyl, with the proviso that when X is other than CH, R_a and Q are deleted,

X'' is an amino β halo C_{1-5} alkylene,

Q is H, C_{1-10} alkyl, C_{1-10} aralkyl, $C(O)R_5Y$ or C(O)Y,

R_5 is an α-amino acid or a peptide comprised of 2 to 5 α-amino acid units,

Y is NHR_4 or OR_4, and

R_4 is H, C_{1-7} alkyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl or 2-pyridylalkyl, and

the α-amino acid or peptide moieties being selected from Groups, A, B, C, C', D, E, E', F, F', G, G', J, K and K', said groups being

A: Lys and Arg

B: Glu, Asp

C: Ser, Thr, Gln, Asn, Cys, His, (3-pyrazolyl)Ala, (4-pyrimidinyl)Ala, and N-methyl derivatives

C': Ser, Thr, Gln, Asn and Cys, and their N-methyl derivatives,

D: Pro, Ind

E: Ala, β-Ala, Leu, Ile, Val, n-Val, β-Val, Met, CHM, β-Valine, β-Alanine, n-Leu and N-methyl derivatives (β-representing beta)

E': Leu, Ile, n-Val, Met, n-Leu, CHM and their N-methyl derivatives,

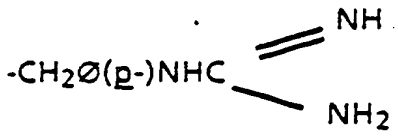
F: Phe, Tyr, CHM, O-Methyl Tyrosine, (3-pyrazolyl)Ala, (4-pyrimidinyl)Ala, Trp, Nal(1), and N-methyl derivatives

F': Phe, Tyr, O-methyl tyrosine, Trp, Nal-(I) and their N-methyl derivatives,

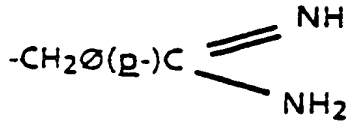
G: Gly, Sar

G': Gly,

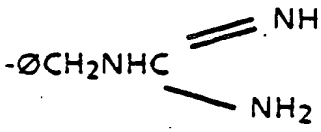
J:



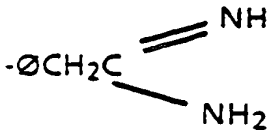
(J-1)



(J-2)



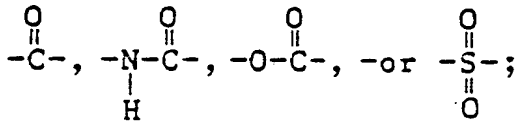
(J-3) and



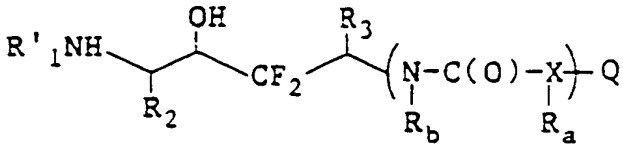
(J-4)

K: Acetyl (Ac), Succinyl (suc), Benzoyl (Bz), t-Butyloxycarbonyl (Boc), Carbobenzoxy (CBZ), Tosyl (Ts), Dansyl (DNS), Isovaleryl (Iva), Methoxysuccinyl (MeOSuc), 1-Adamantanesulphonyl ($AdSO_2$), 1-Adamantaneacetyl (AdAc), 2-Carboxybenzoyl (2-CBZ), Phenylacetyl, t-Butylacetyl (Tba), bis [(1-naphthyl)methyl]-acetyl (BNMA),

K′: is -A-Rz wherein A is

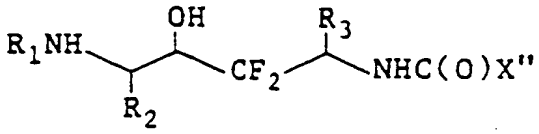


and Rz is an aryl group containing 6, 10 or 12 carbons suitably substituted by 1 to 3 members selected independently from the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido containing from 1 to 15 carbons, provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro, which comprises oxidizing a compound of formulae



A-1

and



B-1

wherein said alcohols of formulae A-1 and B-1 are oxidized by reaction with

(a) an *in situ*-formed sulfonium adduct formed by reaction of dimethylsulfoxide with $(CF_3CO)_2O$ or $(COCl)_2$,

(b) a pyridinium dichromate in the presence of glacial acetic acid,

(c) an *in situ* chromic anhydride-pyridine complex, or

(d) 1,1,1-triacetoxy-2,1-benzoxiodol.

53. A compound according to any one of claims 1 to 49 or a mixture thereof for use as a pharmaceutically active compound.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 89 40 2373

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X Y	EP-A-0 275 101 (MERRELL-DOW) * Whole document * ---	1-49,52-53 50-51	C 07 K 5/02 C 07 K 5/06 C 07 K 5/08 C 07 K 5/10 C 07 K 7/02 C 07 C 311/50 C 07 C 311/51 C 07 C 271/22 C 07 C 271/20 C 07 C 237/22 C 07 C 237/10
X	TETRAHEDRON LETTERS, vol. 29, no. 30, 1988, pages 3687-3690, Pergamon Press plc; D. SCHIRLIN et al.: "A convenient synthesis of alpha' , beta-diamino-alpha, alpha-difluoroketones, new dipeptide isosteres" * Whole article * ---	1,52	
X	WO-A-8 704 349 (DELLARIA et al.) * Pages 42-48; examples 86-106 * ---	1,30-31,53	
Y	CHEMICAL ABSTRACTS, vol. 107, no. 25, 21st December 1987, page 368, abstract no. 231968r, Columbus, Ohio, US; I. KATOH et al.: "Inhibition of retroviral protease activity by an aspartyl proteinase inhibitor", & NATURE (LONDON) 1987, 329(6140), 654-6 * Abstract * ---	50,51	TECHNICAL FIELDS SEARCHED (Int. Cl.5) A 61 K C 07 C C 07 K
Y	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, vol. 85, no. 18, September 1988, pages 6612-6616; S. SEELMEIER et al.: "Human immunodeficiency virus has an aspartic-type protease that can be inhibited by pepstatin A" * Whole article * --- -/-	50,51	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	05-12-1989	MASTURZO P.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 89 40 2373

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	BIOCHEMISTRY, vol. 24, no. 8, 9th April 1985, pages 1813-1817, American Chemical Society; M.H. GELB et al.: "Fluoro ketone inhibitors of hydrolytic enzymes" * Whole article *	1	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	05-12-1989	MASTURZO P.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)